FORMULATION AND EVALUATION OF LANSOPRAZOLE ENTERIC COATED PELLETS

Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University, Chennai-32.

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

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Submitted by

REGISTRATION No. 26103003

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Certificate

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF LANSOPRAZOLE ENTERIC COATED PELLETS",** submitted by the student bearing **Reg.No. 26103003** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND EVALUATION OF LANSOPRAZOLE ENTERIC COATED PELLETS",** submitted to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment to the requirement for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS**, is a bonafide work carried out by **Mr. DIWAKAR MANOHAR PACHABHAI [Reg.No:26103003],** during the academic year 2011-2012,under the guidance and direct supervision of **Mrs.S.BHAMA., M.Pharm.** Asst. Professor, Department of Pharmaceutics**,** J.K.K. Nattraja College of Pharmacy, Komarapalayam.

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DECLARATION

I hereby declare that the dissertation entitled **"FORMULATION AND EVALUATION OF LANSOPRAZOLE ENTERIC COATED PELLETS",** was carried out by me, under the guidance of **Mrs. S.BHAMA., M.Pharm.** Asst. Professor, for submission to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS**. This work is original and has not been submitted in part or full for the award of any other Diploma or Degree of this or any other University. The information furnished in this dissertation is genuine to best of my knowledge and belief.

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DIWAKAR MANOHAR PACHABHAI

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Dedicated to

My Beloved Parents

& Guide

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Introduction

1. INTRODUCTION

ULCER [1]:

A peptic ulcer is a sore in the lining of stomach or duodenum. The duodenum is the first part of small intestine. Peptic ulcers are found in the stomach are called as gastric ulcers, in the duodenum are called duodenal ulcers.

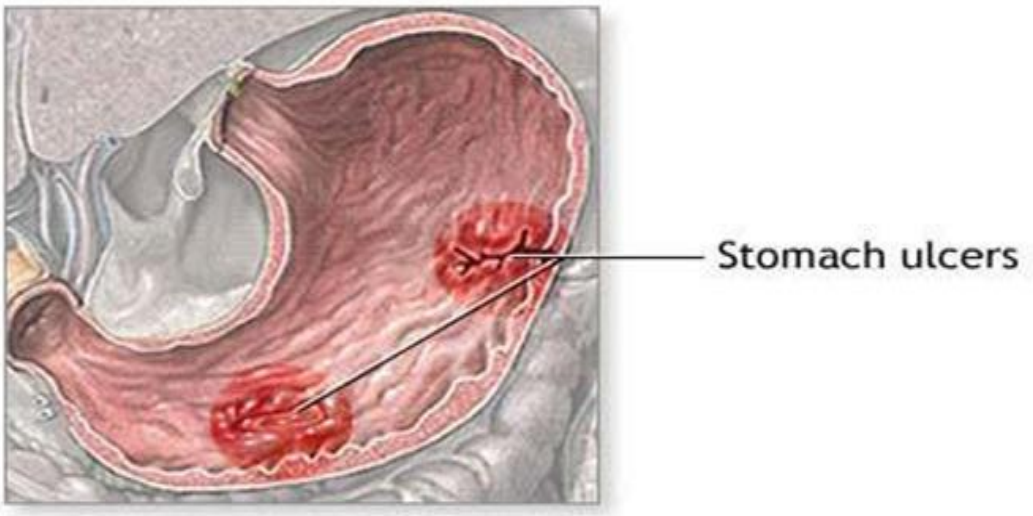


Figure no.1: Peptic ulcer occur in the stomach

Causes of peptic ulcer [2, 3, 4]:

- Peptic ulcers are caused by acid and pepsin (an enzyme) produced in the stomach. Patients who develop ulcers often produce greater amounts of acid than people without ulcers. Also, the ulcer patient may not have strong enough natural defenses in the stomach or intestinal wall to resist the effect of acid and pepsin.
- Doctors do not yet know all the reasons for too much acid production, but many believe the key to healing an ulcer is to control the amount of acid produced.
- Bacteria called *Helicobacter pylori,* or *H. pylori.*
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen

- ***Symptoms of peptic ulcer [2, 3,4]:***
- ***Duodenal Ulcer symptoms:***

1. Pain that awakens patients from sleep.
2. Burning sensation in the upper abdomen.
3. Pain in the back, lower abdomen or chest area may occasionally occur.
4. Pain that occurs when the stomach is empty (about two hours after a meal or during the night).

- ***Gastric Ulcer symptoms:***

1. Gastric ulcer pain may be less severe than duodenal ulcer pain and is noticeably higher in the abdomen.
2. Eating may increase pain rather than relieve pain.
3. Pain is described as aching, nagging, cramping or dull.
4. Other symptoms may include nausea, vomiting and weight loss.

- Some ulcers may produce no symptoms at all. However, occasional painless bleeding, anemia (low blood count), or the passage of black tarry stool may be the first sign of peptic ulcer disease.

Diagnosis of peptic ulcer [4]:

- Diagnosis can often be made from the patient's symptoms.
- X-ray:- The ulcer can be diagnosed by an indentation in the stomach or duodenal wall by using barium.
- Endoscopy – this is a more accurate method of diagnosing ulcer disease in stomach and duodenum with a lighted flexible tube. Gastric ulcers, unlike duodenal ulcers, can occasionally be cancerous. Therefore, endoscopy and biopsy of the gastric ulcer are commonly used for the diagnosis and follow-up of ulcers.

ANTIULCER DRUGS [5, 6]:

The drugs which are used in the treatment of ulcer are called as antiulcer drugs.

Classification of antiulcer drug:

1. Reduction of gastric acid secretion:

a) H_2 Antihistamines: cimetidine, ranitidine, famotidine, roxatidine.

b) Proton pump inhibitor: omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole.

c) Anticholinergic: pirenzepine, propantheline, oxyphenonium.

d) Prostaglandine analogue: misoprostol.

2. Neutralization of gastric acid (antacid).

a) Systemic: sodium biocabonate, sodium Citrate.

b) Nonsystemic: magnesium hydroxide, magnesium Trisilicate, aluminium hydroxide gel, magaldrate, calcium carbonate.

3. **Ulcer protectives:** sucralfate, colloidal bismuth subcitrate.

4. **Anti-H. Pylori drugs:** amoxicillin, clarithromycin, metronidazole, tinidazole, tetracycline.

PROTON-PUMP INHIBITORS [5, 6]:

The proton-pump inhibitors inhibit gastric acid by blocking the H^+/K^+-adenosine triphosphatase enzyme system (the proton pump) of the gastric parietal cell. Examples are omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. omeprazole inhibits cytochrome P450 and lansoprazole is a weak inducer of cytochrome P450. The indications for proton-pump inhibitors include the following:

- Benign duodenal and gastric ulcers.
- NSAID-associated peptic ulcer and gastro-duodenal erosions.
- In combination with antibacterial drugs to eradicate *H. pylori*.
- Zollinger–Ellison syndrome.
- Gastric acid reduction during general anaesthesia, gastro-esophageal reflux disease (GORD).
- Stricturing and erosive oesophagitis where they are the treatment of choice.

Side effect of antiulcer drugs [5, 6]:

Antacids suppress the absorption of other anti-ulcer drugs, tetracyclines, iron pills, etc. affect their efficacy. These two types of drugs should therefore be taken separately, with an interval of one or two hours. Antacids of different formulas may produce mild laxative effect or result in constipation.

INTRODUCTION OF NOVEL DRUG DELIVERY SYSTEM [8, 9]:

Incorporating an existing medicine into a novel drug delivery system (NDDS) can significantly improve its performance in terms of efficacy, safety and improved patient compliance. In the form of a NDDS, an existing drug molecule can get new life, thereby increasing its market value and competitiveness.

Multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits with diameter of 0.05-2.00 mm. To deliver the recommended total dose, these subunits are filled into a capsule or compressed into a tablet. They provide many advantages over single-unit systems because of their small size. Multiparticulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation.

Recently much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

Types of Multipaticulate drug delivery system [8, 9, 10]:

In order to get MPDDS, drug is distributed in small particles (0.05 to 0.2 mm) and then film coated to get desired drug release characteristics.

Different types of Multipaticulate drug delivery system are as follows:-

Drug Crystals

Drug Crystals of appropriate size and shape can be coated directly with a modified release film coating.

Irregular Granules

Granules used in preparation of tablets, can be film coated, irregular shape and variation in particle size make it difficult to achieve uniform coating thickness around each particle.

Spheronized Granules (pellets)

Sphere-shaped particles simplify the coating process. The production of spheroidal particles (pellets) is achieved by extruding the powdered mass, then cutting into small cylindrical particles and finally spheronizing these particles to spherical shape.

Drug-loaded Non-pareils (pellets)

Spherical particles about 1mm in diameter consisting primarily of sucrose and starch called “non-pareils” which are available in the market. Following techniques can be used to get drug loaded non pareils.

- A powder-dosing technique involving alternate dosing of powder (containing drug substance) and binder liquid onto the surface of the non-pareils until the required dose of the drug has been loaded.
- Spray application of drug, either suspended or dissolved in a suitable solvent (usually water) containing a polymer (such as hydroxyl propyl methyl cellulose or polyvinyl pyrrolidone) as a binder onto the surface of the non-pareils.

Mini tablets

Many of the other types of multiparticulates described suffer from two potential batch wise drawbacks, namely:

- Variation in particle size distribution
- Variation in particle shape and surface roughness.

Such variability can results in variable coating thickness and thus product performance. This Problem can be overcome by using mini compressed tablets (size range of 1-2mm) produced using modification of traditional tabletting processes.

Melt-Spray-Congeal Microspheres

Spherical, smooth, 50- to 300-μm particles, typically with embedded API, can be produced by a continuous spinning-disk process

PELLETS [8, 9,10,11,12]*:*

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy. Pellets can be formulated by many ways, the compaction and drug-layering techniques are the most widely used.

Regardless of which manufacturing process is used, pellets have to meet the following Requirements:

(1) They should be near spherical and have a smooth surface; both considered important characteristics for subsequent film coating.

(2) The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical application is considered to be between 600 and 1000 μm.

(3) The pellets should contain high percentage of the active ingredient, maintaining the size of the final dosage form within reasonable limits.

Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio.

Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form. The pelletized products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. The pelletized product can freely disperse in the gastrointestinal tract as a subunit, thus maximizing drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired release pattern.

Advantages of pellets [10, 11]:

- They can be divided in to desired dosage strength without process or formulation changes.
- When pellets containing the active ingredient are in the form of suspension, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms.
- They can also be blended to deliver incompatible bioactive agents.
- They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
- Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule.
- Pellets disperse freely in GI tract, maximize drug absorption, and minimize local irritation of the mucosa by certain irritant drugs.
- ***Improved flow characteristics:*** Spheres have excellent flow properties which can be used in automated processes or in processes where exact dosing is required, e.g. tabletting, moulding operations, capsule filling, and packaging.
- ***Coating:*** Coating of granules is often applied for stabilizing active ingredients in the granule or to control the release of active ingredients. Typical applications in the pharmaceutical industry are the controlled release medicines. The easiest shape to coat is the sphere due to the absence of edges. It is also the most economical one to coat as no extra coating material is required to fill irregularities in the surface of the granules.
- ***Packing of beds and columns:*** In certain processes, porous beds or columns are used as chemical reactors. Spherical particles allow the reproduction of beds with always the same void volume, surface area and permeability. Calculations and predictions of the process characteristics

also become easier when round particles are used as many equations are based on flows around symmetrical bodies.

- ***Density increase:*** Both the true and the bulk density of granules are increased by spheronising. This can improve the process and the packaging.
- ***Marketing:*** For consumer products, spheronising is sometimes only applied for improved product appearance and marketing reasons.
- ***Hardness and friability:*** Hardness and friability depend on the internal cohesive forces and surface characteristics. Spheronization increases the hardness and reduces the friability of granules. This will reduce the amount of fines generated during handling or transportation.

Disadvantages of pellets [10, 11]:

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2mm.

Desirable properties of pellets [10, 11]:

- ***Uncoated pellets:***

1. Uniform spherical shape.
2. Uniform size.
3. Good flow properties.
4. Reproducible packing.
5. High strength.
6. Low friability, Low dust.
7. Smooth surface.
8. Ease of coating.

- ***Once coated:***

1. Maintain all of the above properties.
2. Have desired drug release characteristics.

(a) **(b)** **(c)**

Figure no.2: (a) Pellets, (b) Perfect pellet, (c) Coated pellet.

GROWTH MECHANISM OF PELLETS [12, 13]:

In order to select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. The mechanism of pellet formation and growth, the following steps were proposed:
Nucleation, coalescence, layering and abrasion transfer.

- ***Nucleation:*** Nucleation **(Figure no.3, A)** is a common stage in all pelletization/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates, influence the size, the rate and the extent of nuclear formation. Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation. Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering.

- ***Coalescence:*** Coalescence **(Figure no.3, B)** is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering **(Figure**

no.3, C) is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter. The fines and the fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favorable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

- ***Abrasion transfer:*** In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer **(Figure no.3, D)** which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

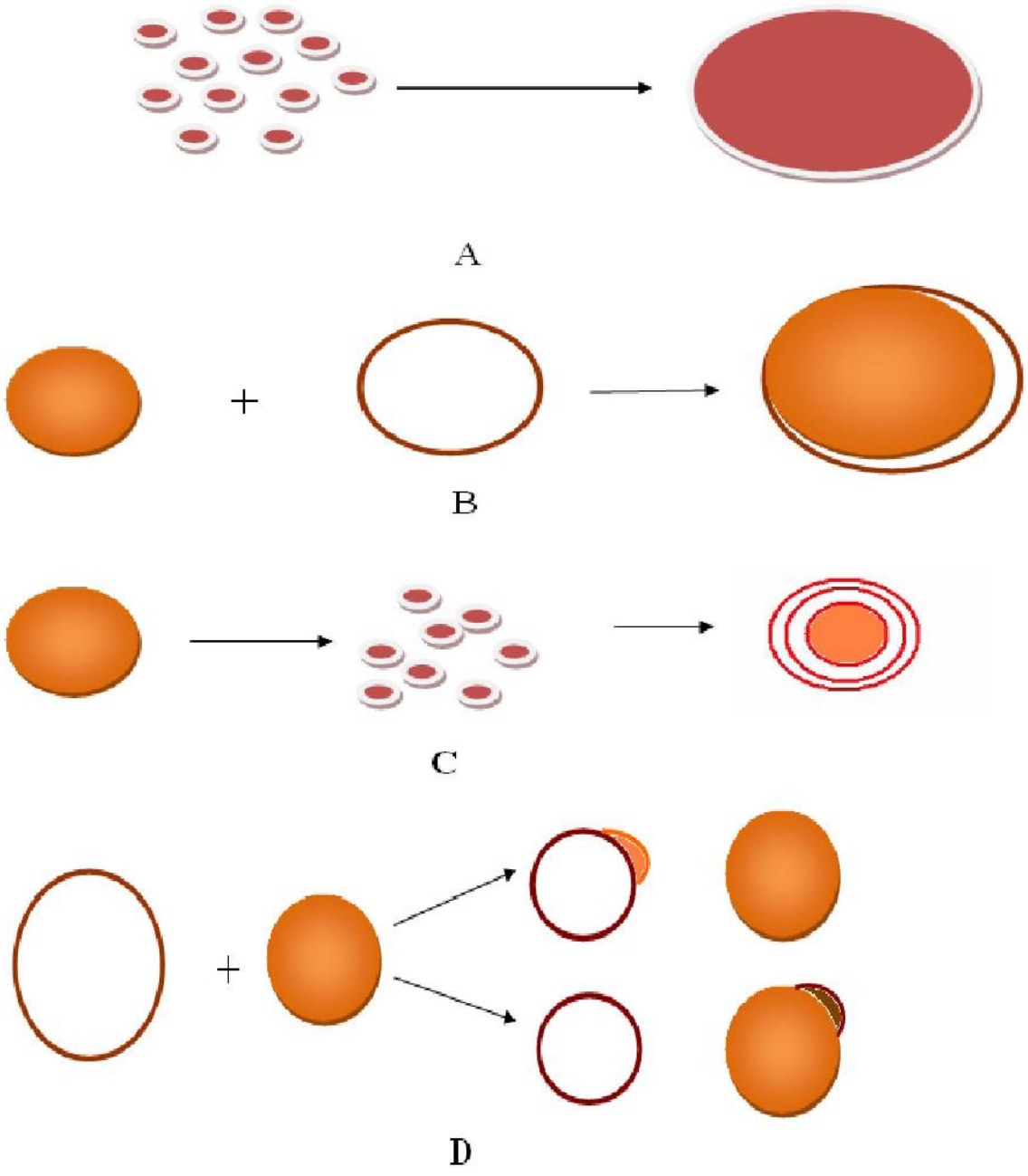


Figure no.3: Pellet growth mechanisms. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer.

PELLETIZATION TECHNIQUES [13]:

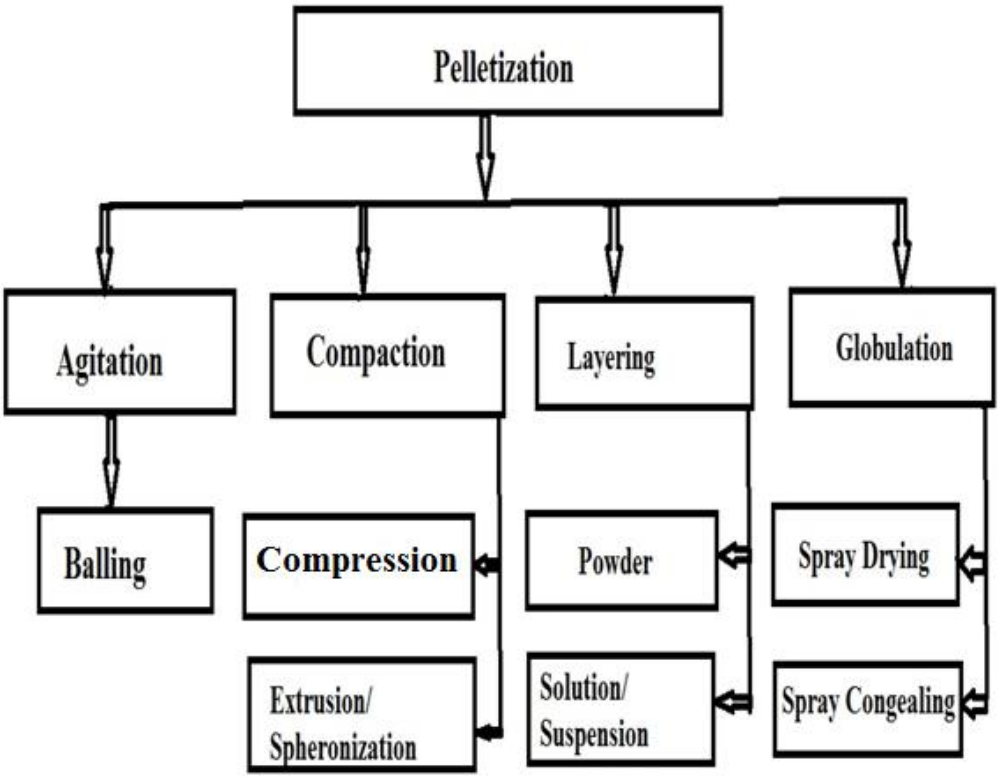


Figure no.4: Different pelletization techniques

Compaction and drug layering are the most widely used pelletisation techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletisation has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletisation methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale.

Extrusion-spheronization [16, 18, 21, 22]*:*

Extrusion-spheronization is a multiple-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution. The granulation step can be performed both in batch-type processors, including a conventional planetary mixer, and vertical or horizontal high-shear and sigma-blade mixers, and in continuous mixers, such as Nica and high-shear twin-screw mixer-extruders. General layout of extrusion spheronization is shown in (**Figure no.5)**.

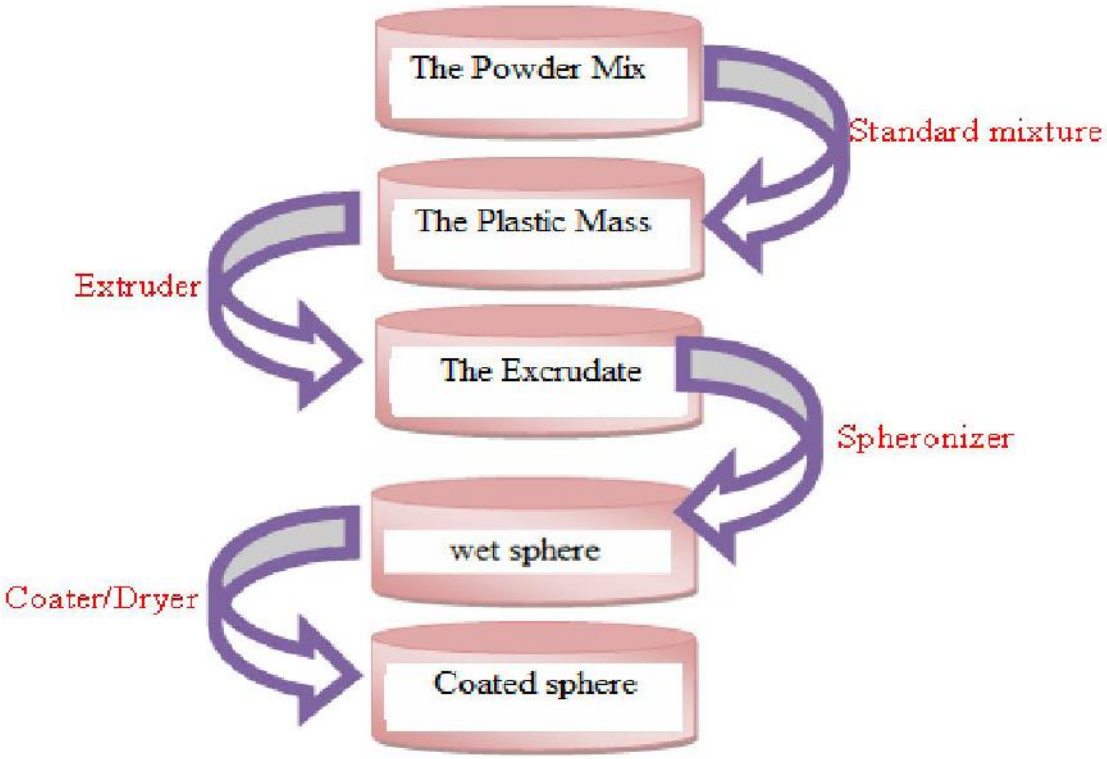


Figure no.5: Extrusion-Spheronisation Process lay out.

Extruders [17, 20]*:*

A variety of extruders are currently on the market, differing in design features and operational principles. These can be classified as screw-fed extruders, gravity-fed extruders, and ram extruders. Screw-fed extruders have screws that rotate along the horizontal axis and hence transport the material horizontally; they may be axial or radial screw extruders **(Figure no. 6)**.

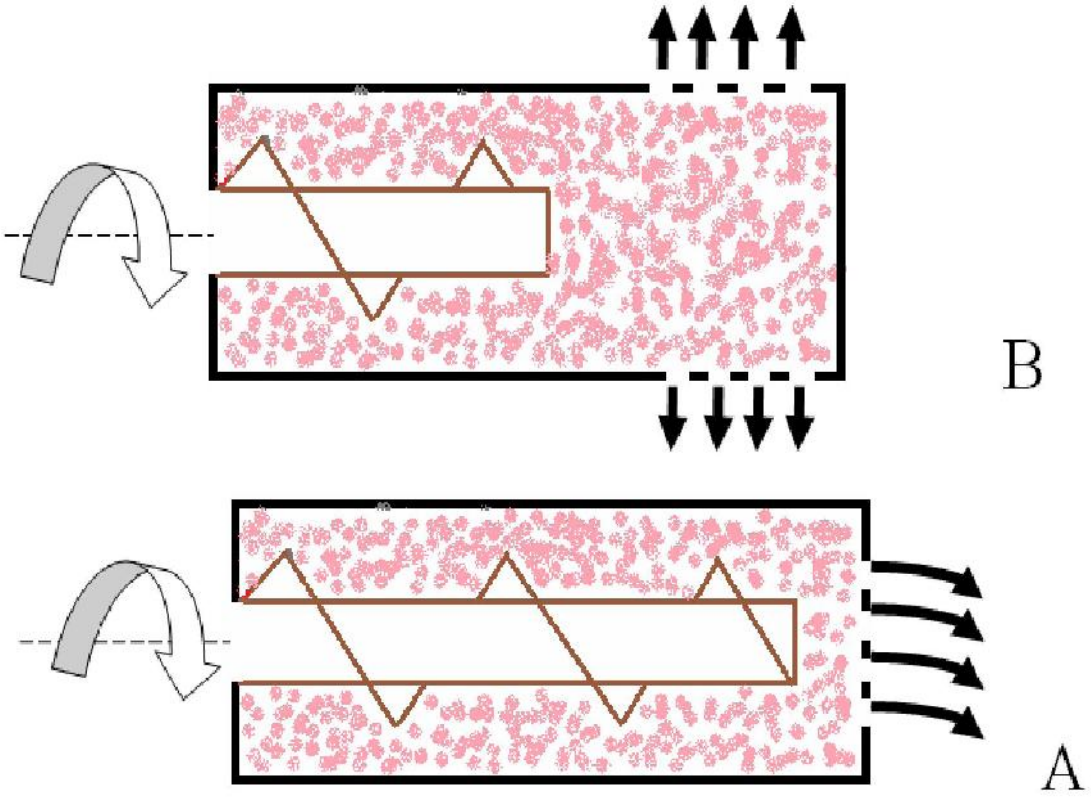


Figure no.6: Screw fed extruders. A: Axial extruder. B: Radial extruder.

Axial extruders which have a die plate that is positioned axially, basically consists of a feeding zone, a compression zone, and an extrusion zone. The temperature of the product during extrusion is controlled by a jacket barrel. In radial extruders, the transport zone is short, and the material is extruded radially through screens that are mounted around the horizontal axis of the screws.

Gravity-fed extruders include the rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter-rotating cylinders **(Figure no.7)**

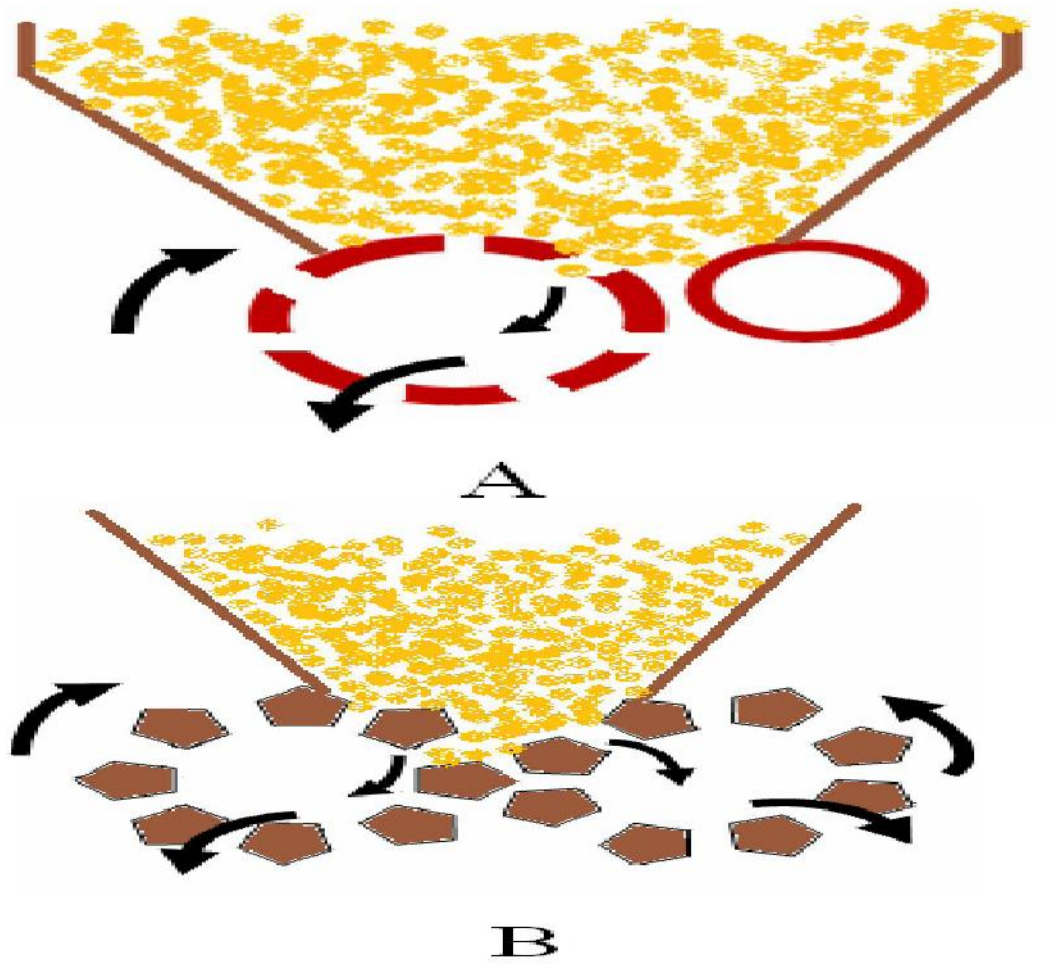


Figure no.7: Gravity fed extruders. A: Rotary-cylinder extruder. B: Rotary-gear Extruder.

In the rotary-cylinder extruder, one of the two counter-rotating cylinders is hollow and perforated; whereas the other cylinder is solid and acts as a pressure roller. In rotary gear extruder, there are two hollow counter-rotating gear cylinders with counter bored holes.

Spheronizer [17, 18, 19, 22]*:*

A spheronizer, known as Marumizer, consists of a static cylinder or stator and a rotating friction plate at the base. The stator can be jacketed for temperature control. The friction plate, a rotating disk with a characteristically grooved surface, is the most important component of the equipment. A standard friction plate with a cross-hatch pattern, where the grooves intersect at a 90^{o} angle, is shown in (**Figure no 8)**.

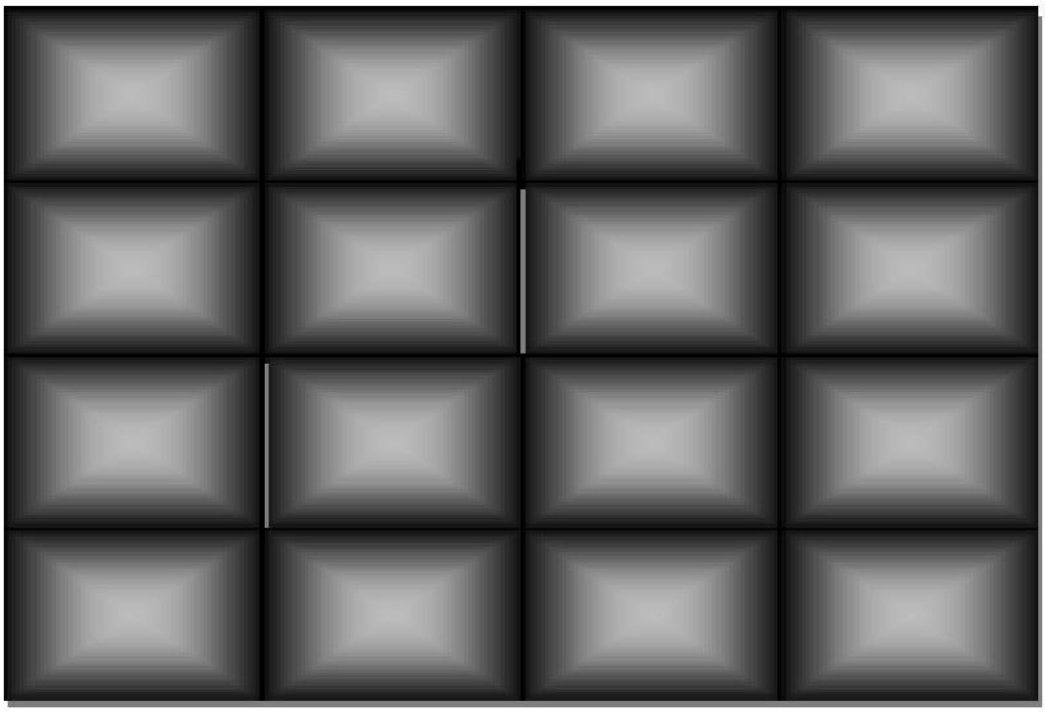


Figure no.8: Spheronizer friction plate with a cross-hatch pattern.

The width of the grooves should be selected according to the pellet diameter, and is, in general, 1.5 to twice the target pellet diameter. The diameter of the friction plate is about 20cm in laboratory-scale equipment and up to about 1m in production-scale units. The rotational speed of the friction plate is variable, ranging from 100 to 2000rpm, depending on the diameter of the unit.

The process produces products ranging from barely-shaped, irregular particles like the conventional granulation, to very spherical particles with drastically different properties. Tabletting characteristics can be altered by modifying the composition, the granulating fluid or the process conditions. The main advantage over other methods of producing drug-loaded

spheres or pellets is the capacity to produce spherical pellets of a uniform size and high drug content up to 90%.

Mechanism of Spheronization [19, 20]:

Following (**Figure no.9)** is the representation of the two models proposed to describe the mechanism of spheronization. The model proposed by Baert et al, describes a transition from initial cylindrical particles (A) into a bent rope (B), dumbbell (C), and two spherical particles wit hollow cavity (D) and spheres (E).

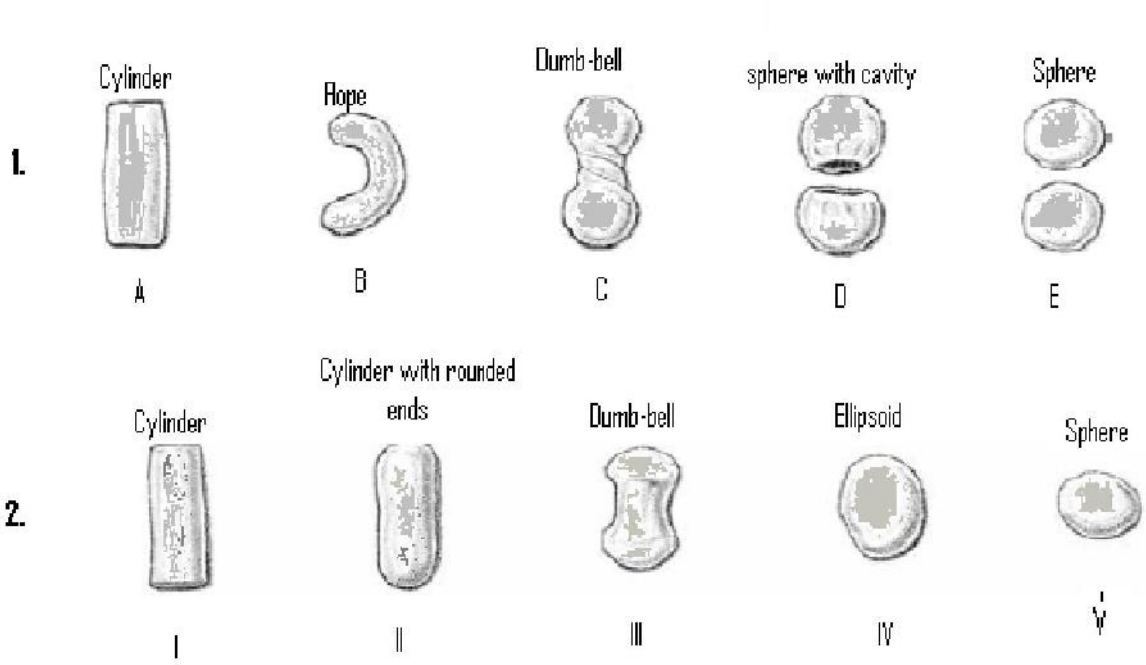


Figure no.9: Mechanism proposed for spheronization

The model proposed by Rowe describes transition from cylindrical particles (F) into cylindrical particles with rounded edges (G), dumbbell (H), Ellipsoid (I) and spheres (J). Thus this graphic representation depicts various stages of pellet formation.

Drug layering [7, 8,9,23]

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei that may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder. (**Figure no.10)** shows principle of powder layering process.

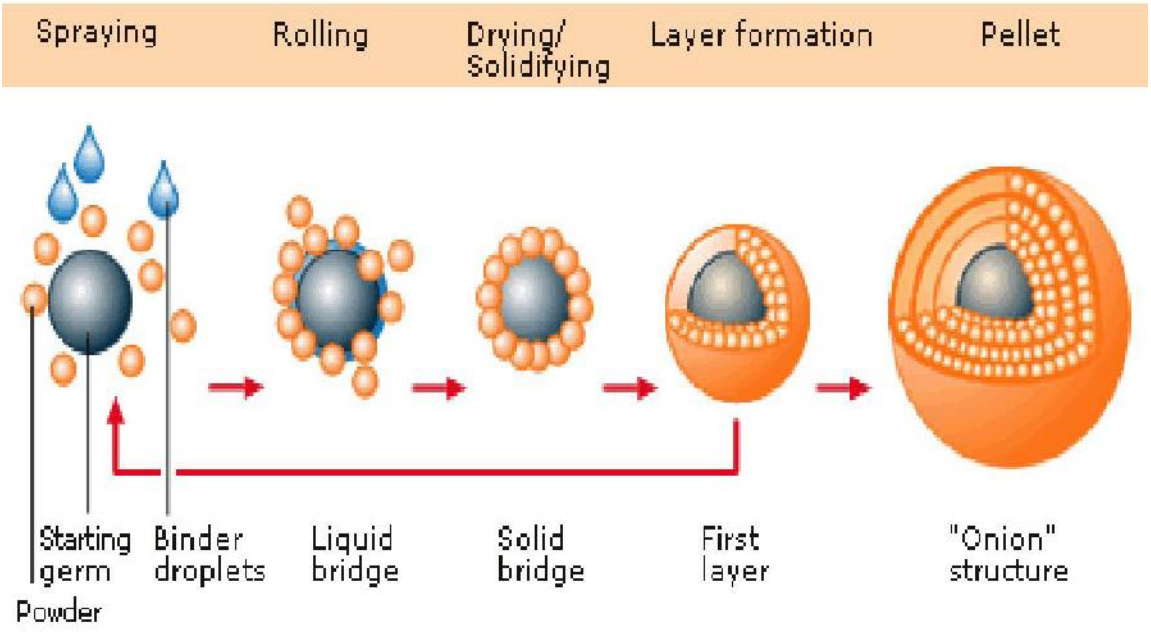


Figure no.10: Principle of the powder layering process

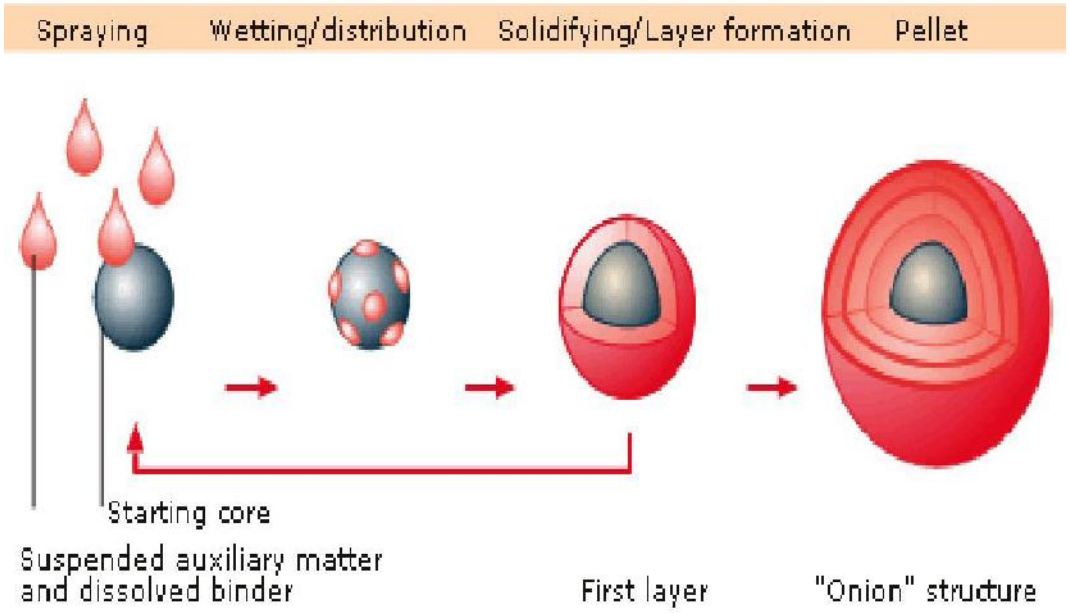


Figure no.11: Principle of the suspension and solution layering process

A starting grain or a pellet can be presented as the starting material. The pellet is built up to the required grain size by adding the layering substance one layer at a time. Powder and binders, suspensions or solutions make suitable layering substances **(Figure no.11)**. The layers are densely applied due to the movement of the pellets in the rotor (Fluid Bed Pelletizing in the rotor). Different layers of various types can be applied. Thick layers can be applied to the starting grains, which, in the case of layers containing active ingredients, allow large amounts of active ingredient to be incorporated.

Conventional pan coaters [23]:

Conventional pan coaters have been used from the very beginning of the history of drug layering pelletisation. From the economic point of view, however, use of conventional pan coaters **(Figure no.12)** is not very reasonable due to the higher labour costs and time consumption, and lower yield.

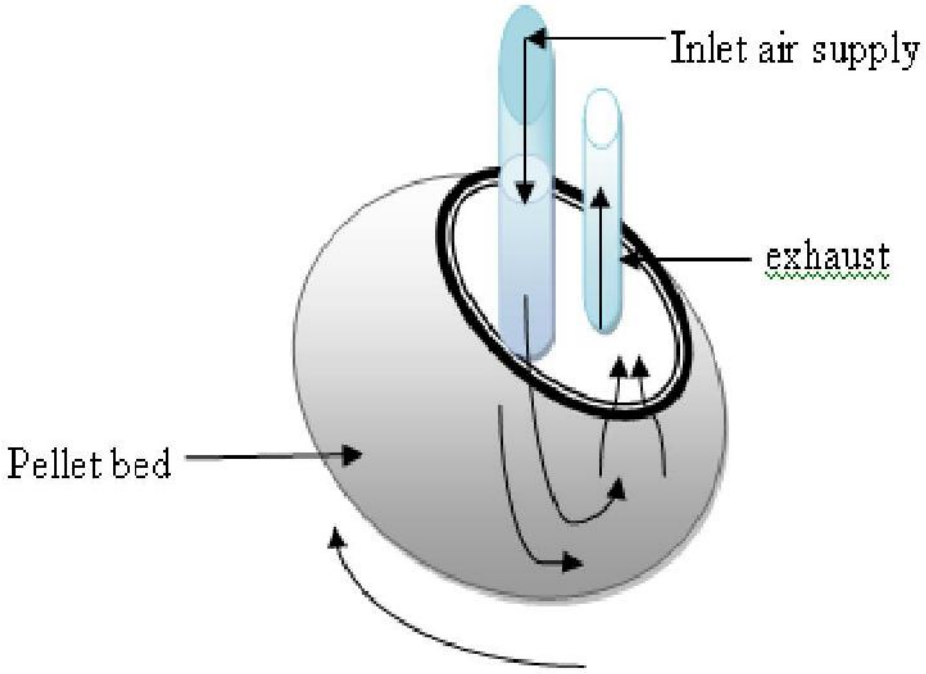


Figure no.12: Conventional Pan Coaters

Fluidized-bed Granulators [26, 27]*:*

High level of perfection in shape and size of the granules can not be obtained by agglomeration mechanism using a conventional fluidized-bed granulator. Modified fluidized - bed units, such as the Roto-processor, the spir-A-flow, and the Glatt Rotor Granulator / Coater (**Figure no.13)**, all utilize a rotating disc at the bottom of fluidized-bed, replacing the airdistribution place. This modification supposedly combines the advantages of the dish granulator and the fluidized bed granulator.

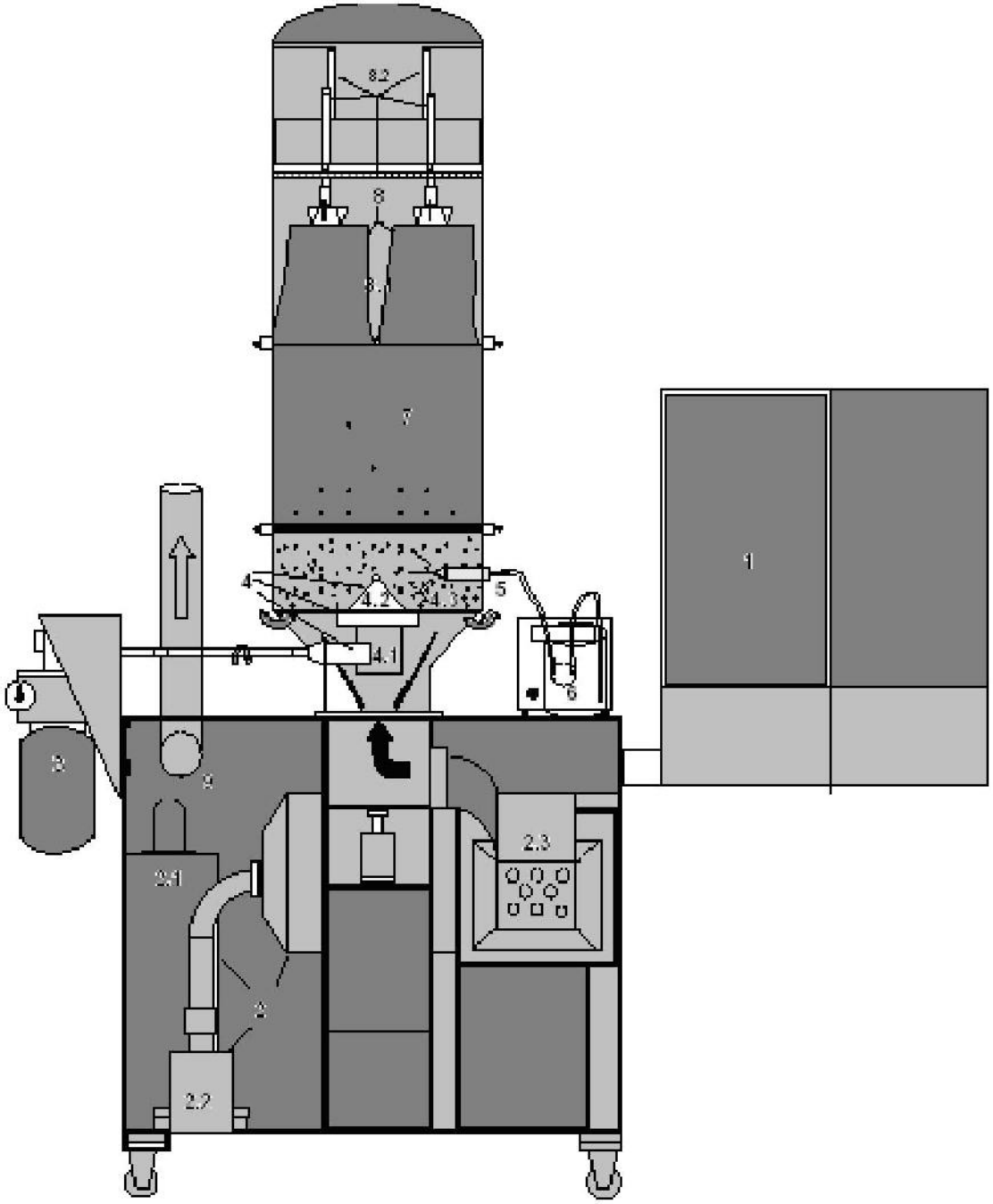


Figure no.13: Glatt rotary fluid-bed spray granulator dryer

Variable in FBP [36]:

Table No.1: Process-Related Variables

a) Inlet air temperature	Higher: finer granules. Lower: Larger, stronger granules.
b) Humidity	Increase in humidity: larger granule size, longer drying times.
c) Fluidizing airflow	Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.
c) Nozzle and nozzle height	A binary nozzle produces finest droplet and is preferred. Optimum nozzle height should cover the bed surface. Too close to the bed: will wet the bed faster, producing larger granules. Too high position: creates finer granules, and increase granulation time.
e) Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size, and granule size. Higher liquid flow rate will produce larger granules and the reverse will produce smaller granules.
f) Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.
g) Rotor Speed	Higher rotation rates resulted in excessive friability of the corers and loss of the coating powder.
h) Spray rate	Lower spray: longer processing time resulting in a lower porosity of the pellets. Higher spray: higher water content, shorter processing time and larger pellets, shorter time for liquid to evaporate, broader size distribution.
i) Moisture content	There is sensitive relation between moisture content and particle size, and moisture sensitivity depends strongly on the formulation, especially the fraction of pelletization aid.

Centrifugal Granulators [24, 25]:

They are routinely used to manufacture pellets by solution, suspension, and powder layering as well as to produce high potency pellets in a few minutes or hours in contrast to the long processing times required in a coating pan process, particularly during powder layering. Centrifugal fluid-bed granulators can be classified as single and double chamber rotary granulators. Most of these granulators utilize a single-walled product chamber with a rotating disc at the base **(Figure no.14)**.

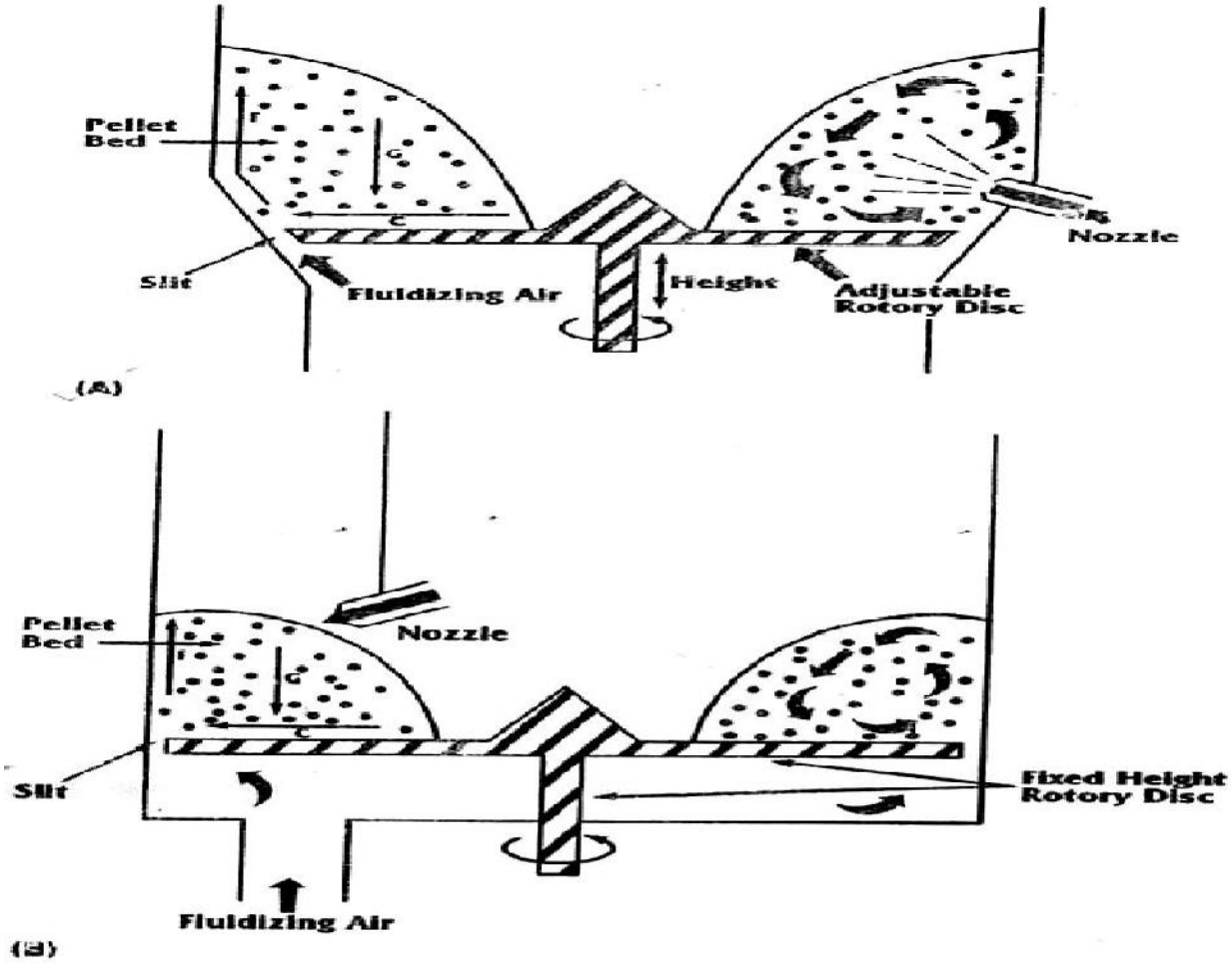


Figure no.14: Centrifugal fluid bed equipments.

Other pelletization methods [28]*:*

Other pelletization methods such as globulation, agitation and compaction (compression) are also used, although in a limited scale, in the preparation of pharmaceutical pellets. Also recently developed techniques like cryopelletization and melt speronization have been employed

Globulation [28, 29]*:*

Globulation, or droplet formation, consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs Principle of spray globulation is depicted in **(Figure no. 15)**.

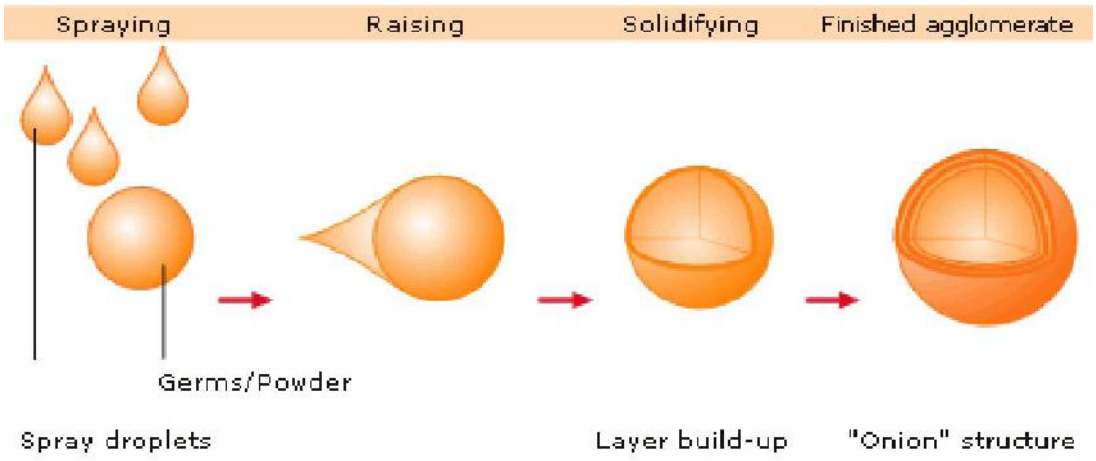


Figure no.15: Principle of Spray Granulation (Globulation)

Compression [28, 29]*:*

Compression is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing.

Balling [28, 29]*:*

Balling is the pelletisation process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid **(Figure no.16)**.

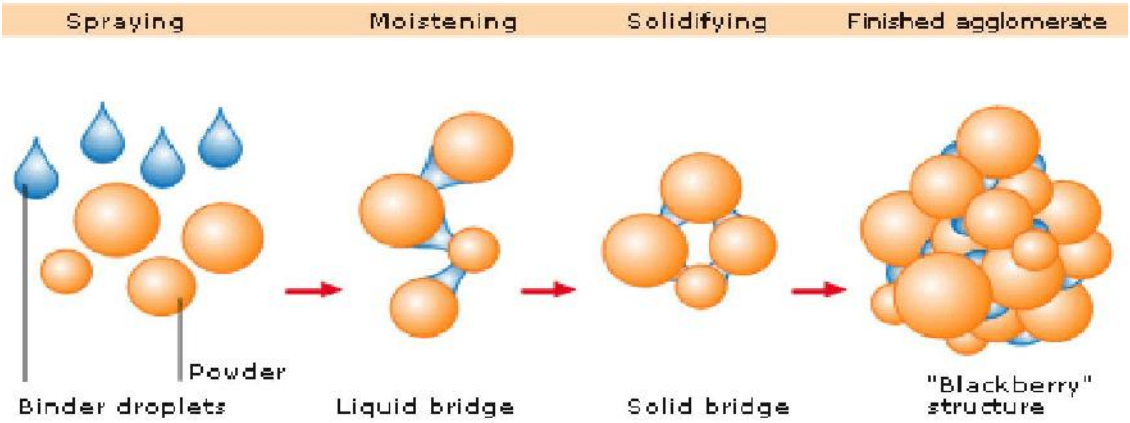


Figure no.16: **Principle of spherical agglomeration (Balling)**

Film-formers for enteric resistance coating [31, 32,33,34,35]*:*

Polymers are macromolecules having a molecular weight range between 10,000 and several million Daltons and consist of a number of repeating units in the structure. They can cause a prolonged drug release in order to extend the intake intervals or enteric resistance in order to protect the drug against the acidic media in the stomach.

Shellac:

The oldest group of polymers for enteric resistance coating, consists only on shellac, which is of natural origin and has been used for hundred years for enteric coatings and taste masking as well as prolonged release. Shellac is obtained from the resinous secretion of the insect Kerria lacca. Due to higher coating levels shellac is able to retard the drug release, but these formulations lack of drug release in the gastric environment. Shellac consists mainly of a mixture of polyesters, basically composed of shelloic and alleuritic acid, which are responsible for its gastric resistance properties. However, as a product of natural origin it is subjected to batch-tobatch variation of the quality in dependence of the purification process and the resulting

content of wax, coloring material and other impurities. According to the literature coating materials such as shellac and resin do not fulfill modern requirements because they are not sufficiently soluble in the digestive tract. Incorporation of hydrophilic polymers into the shellac formulation, according to the study conducted by Qussi and Suess, 2005, could prevent dissolution of drug in simulated gastric fluid for 2 hours and increase the drug release from pellets.

Aqueous dispersion:

Aqueous dispersions are dispersed substances in the dispersing agent, water like gas in water (foam), fluid in water (emulsion), or solid in water (suspension). When the dispersed phase is a polymer, it is called polymer dispersion and the dispersed phase can be solid, fluid or any intermediate condition. The term latex is used for colloidal polymer dispersions. The aqueous systems have an advantage from an environmental standpoint and are less toxic and cheaper than organic systems. The particle size is the most important specification of latex and is between 10 and 1000 nm. Latexes are characterized by low viscosity even when they have high solid content like 30%.

Methacrylic acid copolymers:

Methacrylic acid copolymers belong to a group of polymers which are insoluble in acid media and dissolve by salt formation above pH 5-6. They are full synthetic copolymers exhibiting an acidic carboxyl group which is responsible for the enteric resistance. The backbone is based on a continuous carbon chain stabilized by methyl groups resulting in poly(methyl methacrylate) (PMMA) which was also used crystal clear, unbreakable organic glass.The enteric resistant polymer is available as Eudragit® L and S. Hence they are used for enteric film coatings, since they are insoluble in dilute acids, gastric fluid and pure water, they dissolve in buffer solutions above pH 5.5 (L 100-55), pH 6 (L 100) and pH 7 (S 100). Methacrylic acid copolymers are produced by emulsion polymerization and subsequent spray drying. They are soluble in isopropyl alcohol, acetone, ethanol and methanol, also in mixtures with up to 40% water.

These products are commercially available in the form of spray-dried powders, and in the form of aqueous dispersion with 30% solids (Eudragit L 30 D-55). Eudragit L 30 D-55 is an anionic copolymer based on methacrylic acid and ethyl acrylate, with free carboxyl groups in a ratio of 1:1 with the ester groups. The carboxylic groups begin to ionize in an aqueous media at

pH 5.5 and above, rendering the polymer resistant to the acidic environment of the stomach, but soluble in intestinal fluid. With aqueous dispersions, the process conditions such as spraying rate, drying temperature, amount of drying air and spraying pressure must be carefully chosen because if, as a result of processing conditions, the product bed temperatures are too low, they will be insufficient to achieve the desired filming above minimum film-forming temperature. The product temperature during coating should be approximately 20°C above the minimum film formation temperature in order for good film formation to occur. On the other hand, excessively high product bed temperatures allow the dispersion agent to evaporate so rapidly that the film former is spray dried.

Important reasons for enteric coating are as follows:

- To protect acid-labile drugs from the gastric fluid.
- To protect gastric distress or nausea due to irritation from drug.
- To deliver drugs intended for local action in the intestines.
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed release component to repeat actions.
- Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media (E.g. Esomeprazole, omeprazole, pantaprazole).

Ideal enteric coating materials should have the following properties:

- Resistance to gastric fluids.
- Ready susceptibility to or permeability to intestinal fluids.
- Compatibility with most coating solution components and the drug substrates.
- The film should not change on aging.
- Formation of continuous film.
- Non-toxicity.
- Low cost.
- Ease of application.

Excipients for pellets [32, 33, 34, 35]***:***

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacture of the product. Since pellets are intended to be administered orally, the excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations.

Excipients, disintegrant, surfactants, pH adjusters, Separating agents, Spheronization enhancers, glidants and release modifiers etc. some examples of such excipients are given in Table no.2.

Table No.2: Examples of commonly used excipients

Filler	MCC, Starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, Sucrose, starch
Lubricant	Calcium stearate, glycerin, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
PH adjuster	Citrate, phosphate, meglumine
Surfactant	Polysorbate, Sodium lauryl sulphate
Spherinization enhancer	MCC, Sodium carboxy methyl cellulose
Glidant	Talc, starch, Magnesium stearate
Release modifier	Ethyl cellulose, carnauba wax, shellac

Characterization of pellets [37, 38, 39]*:*

In order to meet the requirements of size distribution, surface area, shape, surface roughness, density and friability, including the reproducibility of morphologic properties of the pellets, pellets have to be tested.

Size distribution [42, 45, 51]***:***

The size distribution of pellets should be as narrow as possible because it will ensure a minimum variation in coating thickness and coating performance within the batch. If the pellets are intended for compression, wide size distribution may lead to segregation and variations in content uniformity. The most common and widely used method for determination of size distribution is *sieve analysis*. The reasons for its extensive use are simplicity, low costs, low time

consumption. Some of the disadvantages of this simple method are the inability of the sieve to detect variation in the shapes of particles. The procedure involves the mechanical shaking of a sample through a series of sieve sizes and weighing these sieves before and after the analysis. Critical parameters of the method are sieve loading, type of motion (vibration or tap), intensity and duration of intensity. Another method for measurement of pellet size distribution is light scattering, and which is most suitable method for spherical particles. In laser diffraction method particles pass through a beam of light, they scatter the light, which is directed onto a diode array detector directly opposite the incident light. Sizing of the particles is based on the angle of diffracted light, with small particles diffracting at wider angles than larger particles. Assuming a log-normal distribution, a plot of particle size versus the cumulative percentage of undersize particles can be used to determine the geometric mean weight diameter *dg*, the size corresponding to the 50% value, which is also equal to the mean diameter Randall, 1995. When making a log-probability plot it is common to find that experimental data are scattered, specially the one with very small and very large particles. For this reason when determining the best straight line, it is recommended by some authors that only experimental points within the 20 to 80% range are used.

Shape and surface roughness [45, 46]***:***

In order to obtain good performance of coated pellets it is necessary to have spherical and smooth particles suitable for subsequent coating, usually for achieving modified-release. The commonly used method is the analysis of microscopic or non-microscopic pictures of interest. Scanning electron microscopy (SEM) is a technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results.

Porosity [45, 46]***:***

The morphology of pellets and total structure can change in any variation in formulation or material properties, affecting porosity, which is considered to have a great influence on coating, flow and packing during tablet or capsule filling Rashid, 2001. It also influences the rate of release of drug from pellets by affecting the capillary action of dissolved drug (Rashid, 2001). The pores can be analyzed, qualitatively, by scanning electron microscopy and, quantitatively by mercury porosimetry. The “PoreSizer” measures the volume distribution of pores in material by mercury intrusion or extrusion. It is a 30,000 psia (207MpA) mercury porosimeter covering the

pore diameter range from approximately 360 to 0.006 μm / 3 nm to 200 μm. The unit has two built-in low pressure ports (range of low pressure measurement 0 to 30 psia which corresponds to pore diameter 360 to 6 μm) and one high pressure chamber (with the high pressure measurement range of 0 – 30 000 psia which corresponds to pore diameter 6 – 0.006 μm). Mercury has a high surface tension and is non-wetting to all materials with exception of a few noble materials. These properties cause a mercury surface in contact with a solid to assume the minimum surface area and the largest radius of curvature possible at a given pressure. An increase in pressure on the mercury shifts the balance between surface tension and surface area causing the radius of the curvature of the mercury contacting the solid to become smaller. When the radius is equal to that of a pore entrance, mercury fills the volume within the pore. The method is based on the capillary rise phenomenon in which excess pressure is required to force a non-wetting liquid into a narrow volume. The mercury is forced into the pores of the sample using an externally applied pressure, with the smallest pores requiring the highest pressure to affect the filling.

Density of pellets [48]:

Variation of density of pellets from batch to batch affects the potency of finished capsules, produces segregation during mixing and causes problems in batch size determination during coating.

Bulk and tap density of pellets is measured using automated tapper, by measuring the volume of a known mass into a graduated cylinder, and is influenced by the diameter and size distribution of pellets. They are indicative of the packing properties of particles. True density indicates the extent of densification or compactness of substance. The pycnometric density is determined by measuring the volume occupied by a known mass of particles which is equivalent to the volume of gas displaced by the particles. In this case only open pores are included in the measured volume since the sealed pores are inaccessible to the gas.

In-vitro dissolution testing [40, 41, 55, 56]:

Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. A dissolution test measures the rate of release of the drug. Before the drug is absorbed from the gastrointestinal tract (GIT), it has to be released and dissolved first. For a development compound, dissolution testing is used primarily to help and evaluate new

formulations by evaluating the drug release from dosage forms, evaluating the stability of these formulations, but for the commercial products dissolution testing is used primarily to confirm manufacturing and product consistency and to assess post-approval changes and the need for bioequivalence studies (Brown et al., 2004).

Friability [49]:

The essential requirement of pellets is to have an acceptable friability to withstand further processing, especially the subsequent coating. A high amount of attrition during the coating procedure could modify the release behavior due to the incorporation of small particles in the film40 friability of less than 0.08% is generally accepted for tablets, but for pellets this value

Flowability [48, 49]:

By angle of repose Θ<25 to 30- excellent Flowability, Θ>40 to 60 - poor flowability.

Chapter-2

Literature Review

2. LITERATURE REVIEW

- ***Fellenius et al, 1981,*** explained Substituted Benzimidazoles Inhibit Gastrointestinal Acid Blocking H.sup.+-ATPase,
- ***Bjorn Wallmark et al, 1985,*** explained the relationship between gastric acid secretion and gastric H^+, K^+, ATPase activity.
- ***Meyer UA. et al, 1996,*** analyzed the metabolism of proton-pump inhibitors lansoprazole, omeprazole and pantoprazole by cytochrome P450 (CYP) enzymes, and consequences for drug-drug interactions.He concluded that Proton-pump inhibitors interact with and are metabolized by several human cytochromes P450, but only pantoprazole is also metabolized by a sulfotransferase. This may partlt explain why, in this group of proton-pump inhibitors, pantaprazole has the lowest potential for interactions with other drugs.
- ***Fryklund et al, 1988,*** studied the Function and Structure of Parietal Cells After $H.^+$ /K^+-ATPase Blockade,
- ***Sean R. Tunis et al, 1997,*** compared **"**Lansoprazole with $histamine_2$-receptor antagonists in healing gastric ulcers: A meta-analysis" shows that lansoprazole heals ulcer more quickly than do the H_2RAs and also achieved higher overall rates of healing.
- ***Jae-Wook Ko et al, 1997,*** Evaluated of Omeprazole and Lansoprazole as inhibitors of cytochrome P450 isomers.
- ***Hasebe T et al, 1998,*** investigated of the differences in background factors, clinical features, and gastric function tests among gastric ulcers of various depths. They concluded that smoking, alcohol consumption, recurrence of ulcers, hyperacidity and H.pylori infections are important factors associated with deep ulcers.
- ***M. Marvola et al., (1998),*** developed a multiple unit site specific drug formulation allowing targeting of drug release in the colon by enteric polymer as binders and coating materials. Ibuprofen and furosemide were the model drugs. Methacrylate copolymer, hydroxpropyl methylcellose acetate succinate and cellulose acetate phthalate were used as enteric polymer. The main conclusion was that drug release can be targeted on the distal part of the small intestine and the colon by preparing film-coated matrix pellets in which enteric polymers dissolving at PH have been used both as binders in the pellets and as coating material.

- ***US Patent by Lundberg et al, 2000,*** explained new pharmaceutical dosage form comprising a core material that contains a proton pump inhibiter, one or more alkaline reacting compounds and optionally pharmaceutical excipients having a water soluble separating layer and an enteric coating layer.
- ***J. Jaime Caro et al, 2001,*** explained Healing and relapse rates in gastroesophageal reflux disease treated with newer proton-pump inhibitors Lansoprazole, Rabeprazole and pantoprazole compaired with omeprazole, ranitidine and placebo: evidence from randomized clinical trials.
- ***Robinson M. et al, 2001,*** studied 'New-generation proton pump inhibitors: overcoming the limitations of early-generation agents,When the two newest PPIs, rabeprazole and esomeprazole, are compared with the old drugs in this class (omeprazole, lansoprazole and pantoprazole), the newer PPIs offer several key advantages over older agents, particularly in terms of the management of gastro-esophageal reflux disease. Rabeprazole and esomeprazole achieve more rapid and profound inhibition of acid secretion than do older agents, and they sustain this suppression to provide acid control and symptom relief over 24h.
- ***Gerson et al, 2001,*** studied Protonpump inhibitors and their drug interactions: an evidence based approach.
- ***Us Patent By Hsiao et al, 2002,*** explained method for preparing an oral formulation consisting acid sensitive drugs, including at least the following step : spreading a solution or a suspension containing at least stabilizers, solvents and acid sensitive drugs or its pharmaceutically acceptable salts on to a core made from one or more excipients , and then drying the core to make an active ingredients layer over the core.
- ***Anan S. Raghunath et al, 2003,*** explained the clinical and economic impact of using Esomeprazole or Lansoprazole for the treatment of erosive esophagitis.
- ***Us patent By Chen, 2004,*** investigated New stable enteric coated pharmaceutical dosage form for oral use containing omeprazole or lansoprazole, to a formulation and a method for the manufacture of such a dosage forms, and to a method of gastric acid pump inhibition and providing gastrointestinal cytoprotective benefit by using them.
- ***Stephen Levine et al, 2004,*** explained the use of Acrylic resins for improved aqueous enteric coating.

- ***J.W.Devlin et al, 2005,*** explained **'**Proton pump inhibitors for acid suppression in the intensive care unit: Formulary considerations'
- ***John W Devlin et al, 2005,*** used an evidence-based approach, the linical efficacy, safety, and cost-effectiveness of proton pump inhibitors (PPIs) for treatment of common acid peptic disorders in the acutely ill and provide clinicians with guidance when making hospital formulary decisions with this class of agents. They conclude while the introduction of new proton pump inhibitor products has expanded the therapeutic options for acid suppression in acutely ill patients, a number of unresolved significance of one PPI formulation over the other, and how oral/enteral therapy should be used as step-down therapy after parenteral therapy.
- ***D. Sreedhar et al, 2001,*** introduced Proton Pump Inhibitors, for the treatment of heartburn, ulcers and Gastroesophageal reflux disease (GERD).
- ***Vinod P. Shah et al***, explained dissolution profile comparison and its impact.
- ***Harun Ar Rashid et al.,*** studied the influence of the centrifugal granulating process on the properties of layered pellets. The study was to characterize the effect of three variables that is rotor rotation speed slit air flow rate and spray air rate on the properties of the drug layered pellets prepared with MCC beads as substrates using 33 full factorial experimental design. The responses studied were the amount of drug loss during the process and the amount of agglomerates, bulk density, flowability, as well as the shape and surface roughness of the pellets.
- ***Wong DT, Robertson DW, Bymaster FP, Krushinski JH, Reid LR.,*** worked on influence of subcoat application and micro-environmental pH on the dissolution properties of enteric coated sodium valproate pellets was investigated. The pellets were prepared by solution-layering or wet-mass extrusion-spheronization methods. In order to pass the USP enteric test, the solution-layered and wet-mass extruded pellets required 35 and 25% weight gain of EudragitL 30D-55, respectively. The application of a subcoat of either Methocel-E5 (HPMC) or Opadry AMB to the pellets resulted in a delay in sodium valproate release in 0.1N HCl. Further delay in drug release was observed when citric acid was present in a HPMC subcoat or when added to the core pellet formulation. The amount of drug released from coated pellets was a function of the level of citric acid in the pellet core or subcoat and subsequent micro- environmental pH of the pellets. Citric acid exerted a plasticizing effect on the enteric

polymer film and improved film formation and polymer coalescence. When greater than 10% (w/w) citric acid was present in the pellets, a decrease in drug content was observed due to the conversion of sodium valproate to the volatile compound, valproic acid. Pellets containing less than 10% (w/w) citric acid maintained potency during processing31.

- ***Md A Rahman, J Ali et al,*** studied the multiparticulate formulation of sodium para aminosalicylate for oral administration was developed by extrusion spheronization technique. Microcrystalline cellulose was used as filler in concentration of 14.4% w/w. Pellets were coated with Eudragit L 30 D-55 using fluidized bed processor. Different weight gains of acrylic polymer were applied onto the pellets and evaluated for *in vitro* dissolution behavior in 0.1 N HCl for two hours and then media was changed to phosphate buffer pH 6.8. A 60% w/w coating level of Eudragit L30 D 55 has produced the most acceptable results against the gastric attack. 3% Seal coat of HPMC E5 was also applied in order to protect the drug from migration into the Eudragit coat and film coat was applied in order to prevent aggregation of pellets in the dissolution media. Morphological characteristics of developed pellets were also investigated by scanning electron microscopy and found to be smooth and spherical. Developed system was found to be suitable for the delivery of Sod PAS in to intestinal region39.
- ***MC Gohel, KG Sarvaiya et al,*** explained the objective of the present work was to formulate the enteric minitablets of isoniazid by cold extrusion method. The minitablets were prepared using isoniazid, hydroxylpropylmethylcellulose phthalate and dibasic calcium phosphate. The minitablets were coated using hydroxypropylmethylcellulose phthalate. Full factorial design was adopted to optimize the formulation. The minitablets showed good flow and acceptable friability. The drug release was resisted in 0.1 N HCl for 2 h from the optimized batch. The optimized batch showed more than 90% of drug release in phosphate buffer in 15 min. Capsules containing rifampicin powder and enteric isoniazid minitablets showed complete drug release in acidic and alkaline media respectively. The process of cold extrusion appears to be an attractive alternative to by-pass the existing patents38.
- ***S. C Basak, K Kaladhar, T Subburaj et al,*** reported a delayed release doxycycline hyclate capsules were prepared with suitable blend of doxycycline hyclate-coated nonpareil seed pellets and doxycycline hyclate delayed release pellets. The delayed release pellets were prepared by coating the doxycycline hyclate-coated pellets with

hydroxypropylmethylcellulose phthalate-55 polymer solution. A concentration of polymer in the range of 15 to 20% was found to comply with drug release test as specified in the USP in acid medium but failed to meet the requirements in buffer medium (pH 5.5). The inclusion of sodium starch glycolate (1-3%) in both doxycycline-coated and delayed release pellets preparation stages was found to enhance the release of the drug in the buffer medium without altering its release in acid medium. The blend of delayed release pellets (75%) and drug-coated pellets (25%) in delayed release doxycycline hyclate capsules produced an optimum in vitro drug release in both the media.

- ***Lin. et al. (2004),*** studied hydrophilic excipient like HPMC, spray-dried lactose modulate the time lag of time-controlled disintegrating press-coated tablet. They reported that the lag time markedly dependent in the weight ratio of Ethyl cellulose (EC)/ spray dried lactose or EC/HPMC in the outer shell. Different time lags of the press coated tablets from 1 to 16.3 hours could be modulated by changing the type and amount of excipients. A semi logarithmic plot of the time lag of the tablet against the weight ratios of (EC)/SDL or EC/HPMC in the outer shell demonstrated a good linear relationship, with r = 0.976 and r = 0.982, respectively.
- ***Bai et al,(2005),*** invented a pulsatile drug delivery system comprising of plurality of particle that are divided in to several individual delivery units, each having it's own distinct composition. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release. The individual particles had the same composition of internal core, but the thickness of the external coating layer varied.
- ***J. Siepmann. et al., 2007,*** studied the use of polymer blends as coating material for controlled drug delivery system and their advantages. But these systems are more complex than coatings based on only one polymer. The blended polymers can be incompatible and care has to be taken using these types of formulations.

Chapter-3

Aim and Objective

3. AIM AND OBJECTIVE

AIM OF THE STUDY

The aim of the present study was to formulate anti ulcer drug Lansoprazole as a delayed release multiple unit particulate system (pellets) and study the *invitro* release pattern.

Anti ulcer drugs under the category of proton pump inhibitor are acid labile drugs. These drugs will degrade in acidic environment and will lead to therapeutic inefficacy. It is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers.

Lansoprazole is a acid labile drug and it will degrade in acidic environment. Therefore to bypass the acidic pH of the stomach Lansoprazole is formulated as enteric coated pellets.

The present work was carried out for preparation of lansoprazole enteric coated pelletes to prevent drug release in stomach.

OBJECTIVE

- The objective of the work is to develop a stable, pharmaceutically equivalent, robust and delayed release pellet formulation of Lansoprazole, which is an orally administered antiulcer drug
- Pellets are of great interest to the pharmaceutical industry for variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents.
- To formulate and evaluate multiple unit particulate system of anti ulcer drug.
- To study the release profile of the dosage form and to compare their drug-release profiles with the innovator.
- To study the stability of dosage form.

Chapter-4

Plan of Work

4. PLAN OF WORK

Present work was carried out to design and evaluate the enteric coated pellets of Lansoprazole.

The study was proposed to carry out in the following stages

Phase-1

- Preformulation study of lansoprazole
- Preparation of standard curve of lansoprazole

Phase-2

- Formulation of enteric coated pellets
- Evalution of enteric coated pellets
  - Friability test
  - Bulk and Tapped Density
  - Angle of repose
  - Particle size determination
  - Assay study
  - Gastric acid resistant test
  - *Invitro* Dissolution study
  - Scanning electron microscopy
- Comparison study with marketed formulation.

Phase-3

- Accelerated stability studies.

Chapter-5

Drug and Excipient Profile

5. PROFILE

DRUG PROFILE:

LANSOPRAZOLE [5, 6,58,59,60]:

Appearance:

Lansoprazole is a white to brownish-white odorless crystalline powder.

Chemical IUPAC Name:

2-[(3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl) methylsulfinyl] -1*H*-benzoimidazole.

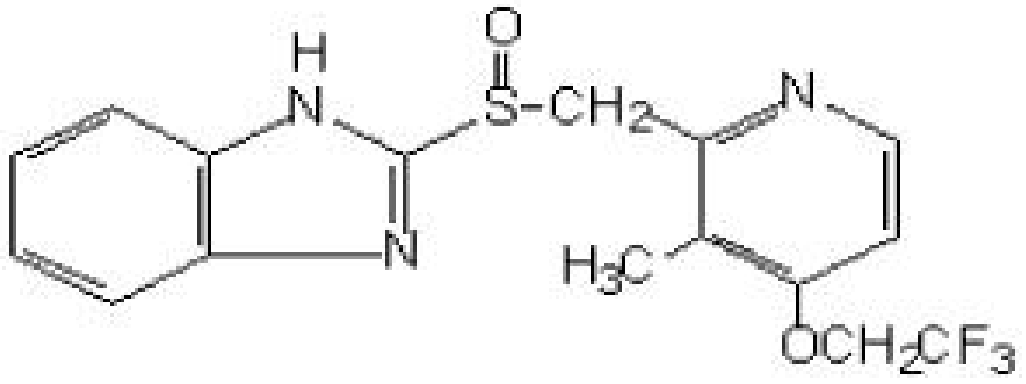
Chemical Formula:

$C_{16}H_{14}F_3N_3O_2S$

Molecular Weight:

369.363

Molecular structure:



Solubility:

Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Melting point:

178-182 ^{o}C

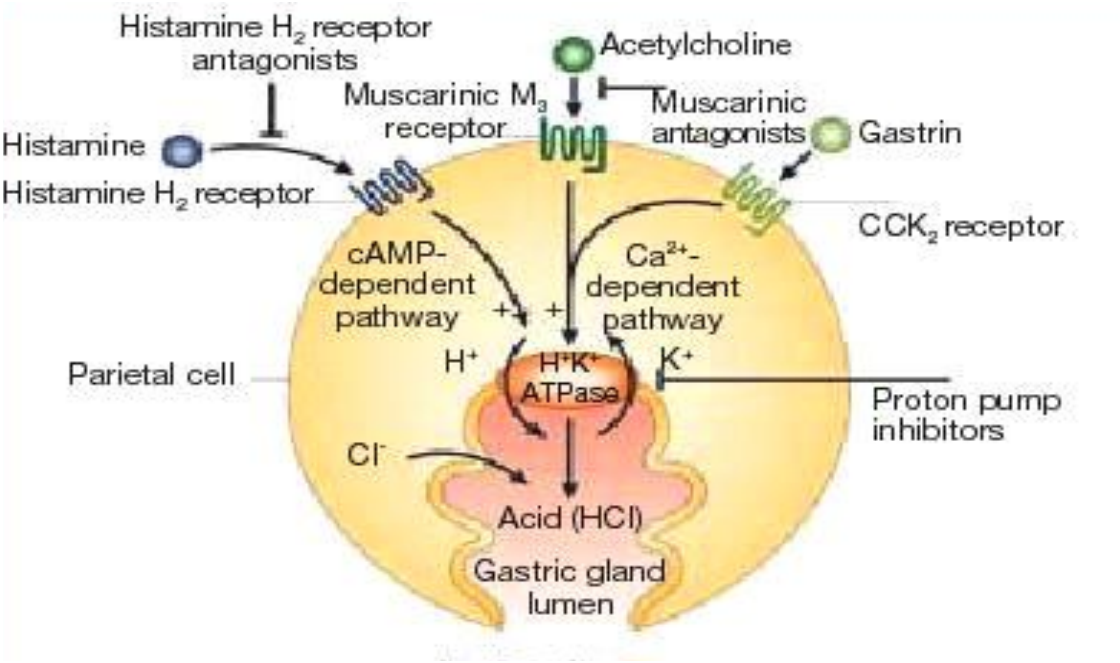
Half life:

1.5 (± 1.0) hours

Pharmacology of lansoprazole

Mechanism of Action:

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but rather suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, Lansoprazole has been characterized as a gastric acid-pump inhibitor which blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.



Pharmacokinetics:

Absorption:

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%.

Distribution:

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 µg/ml.

Metabolism:

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H^+, K^+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Excretion:

Following single-dose oral administration of Lnsoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Side Effects:

Lansoprazole is well tolerated. A low incidence of events has been reported during clinical trials in 7867 patients treated with lansoprazole. These events, which are generally transient and self limiting, include headache, fatigue, malaise, diarrhoea, abdominal pain, dyspepsia, nausea, vomiting, dizziness, constipation, flatulence, dry or sore mouth or throat, rash, upper respiratory tract infections, urinary tract infections, arthalgia, and myalgia. Dermatological reactions include urticaria and pruitus. These generally resolve on discontinuation of drug therapy. Serious dermatological reactions are rare but there have been occasional reports of erythematous or bullous rashes including erythema multiforme. Cases of hair thining and photosensitivity have also been reported. Other reported reactions include jaundice, hepatitis, interstitial nephritis (sometimes resulting in renal failure.), anaphylaxis, wheezing, angioedema, bruising, purpura, petechiae, depression, peripheral oedema, paraesthesia, blurred vision, taste

disturbance, vertigo, confusion and hallucinations. Gynaecomastia and impotence may occur with long term use. During clinical trials a small number of patients developed abnormal liver function tests while on lansoprazole, however routine monitoring of liver function tests is not required.

Overdose:

There is no information on the effect of acute over dosage. In case of overdose, supportive and symptomatic therapy should be initiated.

Dosage up to 180 mg/day for more than a year has been used to treat Zollinger Ellison Syndrome with no serious adverse effects.

Uses:

- Anti-Infective Agents
- Anti-Ulcer Agents
- Enzyme Inhibitors
- Proton-pump Inhibitors.

EXCIPIENT PROFILE

SUGAR SPHERES [33, 34]*:*

Non Proprietary Names:

BP: Sugar Spheres ; PHEUR: Sacchari sphere,USP : Sugar Spheres.

Synonyms:

Non-Pareil, Non-Pareil seeds, NPTAB, Nu-Core, Nu-Pareil PG, Sugar seeds, Suglets.

Description:

The USPNF23 describes sugar spheres as approximately spherical granules of a labeled nominal size range with a uniform diameter & containing not less than 62.5% and not more than 91.5% of sucrose, calculation on dried basis.

Category:

Tablet and Capsule diluents.

Density:

1.57-1.59 g/cm3for suglets less than 500 μm in size. 1.55-1.58 g/cm3for suglets more than 500 μm in size.

Solubility:

Solubility in water varies accordingly to the sucrose to starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

Flowability:

<10 seconds, free flowing.

Applications:

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, practically multiparticulate sustained release formulations. Sugar spheres are also used in confectionery products.

Stability and Storage:

Sugar spheres are stable when stored in a well closed container in a cool dry place.

Incompatibility:

Metals, which can lead to incompatibility with active ingredients Eg: Ascorbic acid. Sucrose may also be contaminated with sulfite from the refining process. In the presence of dilute or concentrated acids,sucrose is hydrolyzed or inverted to dextrose and fructose (Invert sugar). Sucrose may attack aluminium closures.

EUDRAGIT L30 D-55 [31, 34, 61]*:*

Non Proprietary Names:

Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30 Per Cent" Ph. Eur. "Methacrylic Acid Copolymer Dispersion" USP/NF "Methacrylic Acid Copolymer LD" JPE

Chemical Name:

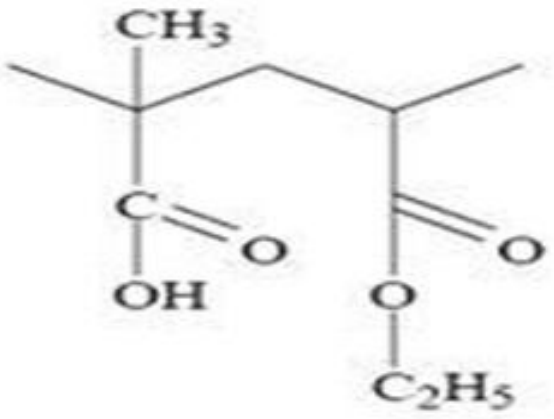
Poly (methacylic acid-co-ethyl acrylate) 1:1

Molecular Weight:

250,000.

Structural formula:

EUDRAGIT® L 30 D-55 is the aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate.



The ratio of the free carboxyl groups to the ester groups is approx. 1:1.

Category:

Film former; tablet binder; tablet diluent.

Description:

Milky-white liquid of low viscosity with a faint characteristic odour.

PH:

2.1 - 3.0.

PURITY:

Sulphated ash / Residue on ignition:

Max. 0.12 % according to Ph. Eur. 2.4.14 or USP <281>. 1 g EUDRAGIT® L 30 D-55 is used for the test. Max. 0.10 according to JPE. 2 g of EUDRAGIT® L 30 D-55 are used for the test.

Heavy metals:

Max. 20 ppm according to Ph. Eur. 2.4.8 method C or USP <231> method II. 1 g EUDRAGIT® L 30 D-55 is used for the test.

Arsenic:

Max. 1 ppm according to JP method 3, Apparatus B. 2.0 g EUDRAGIT® L 30 D-55 are used for the test.

Monomers:

Max. 100 ppm according to the Ph. Eur. or USP/NF monographs.

Microbial count:

Max. 1,000 CFU / g; Salmonella not detectable in 10 g, E. coli, S. aureus, Ps. aeruginosa not detectable in 1 g. The test is performed according to Ph. Eur. 2.6.12 and 2.6.13.

Characteristics:

Polymethacrylates are primarily used in oral capsules,&tablet formulations as film coating agents. Effective and stable enteric coatings with a fast dissolution in the upper bowel. Granulation of drug substances in powder form for controlled release. Site specific drug delivery in intestine by combination with EUDRAGIT L30 D55 grades.

Solubility:

The dispersion is miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part EUDRAGIT® L 30 D-55 with 5 parts acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol; initially, the polymer is precipitated, but then dissolves again in the excess organic solvent. A clear or slightly cloudy liquid is obtained by mixing 1 part EUDRAGIT® L 30 D-55 with 2 parts 1 N sodium hydroxide.

Stability&Storage:

Minimum stability dates are given on the product labels and batch-related certificates of Analysis.

Protect from warm temperatures (USP General Notices). Protect from freezing. Avoid contamination during sampling. Containers that have been opened for use should be closed again immediately and the content used up within the next few weeks.

Incompatability:

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent.

HYDROXYPROPYL METHYL CELLULOSE [31, 34]:

Synonym:

Hypromellose, Hypromellosum, Methocel.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Functional category:

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Melting point:

190–200°C, Glass transition temperature is 170–180°C.

Stability and storage condition:

It is a stable material, although it is hygroscopic after drying.Solutions are stable at pH 3–11. It should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety:

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

Application:

It is widely used in oral, ophthalmic and topical pharmaceutical formulations.

TITANIUM DI-OXIDE [34, 35, 61]:

Synonym:

Anatase titanium dioxide; brookite titanium dioxide; color index number 77891; E171; *Kronos 1171*; pigment white 6; rutile titanium dioxide; *Tioxide*; *TiPure*; titanic anhydride; *Tronox*.

Description:

White, amorphous, odorless, and tasteless nonhygroscopic powder.

Functional category:

Coating agent; opacifier; pigment.

Solubility:

Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water. Soluble in hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolonged heating produces a less-soluble material.

Melting point:

185°C

Stability and storage condition:

Titanium dioxide is extremely stable at high temperatures. This is due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions.

Titanium dioxide should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities:

Owing to a photocatalytic effect, titanium dioxide may interact with certain active substances, e.g. famotidine.

Safety:

Titanium dioxide is widely used in foods and oral and topical pharmaceutical formulations. It is generally regarded as an essentially nonirritant and nontoxic excipient.

Application:

Titanium dioxide is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules. Titanium dioxide may also be admixed with other pigments.

TALC [34, 35, 61]:

Synonym:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; *Luzenac Pharma*; magnesium hydrogen metasilicate; *Magsil Osmanthus*; *Magsil Star*; powdered talc; purified French chalk; *Purtalc*; soapstone; steatite; *Superiore*.

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and storage condition:

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Safety:

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material.

Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.

Application:

Talc is used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent.

PEG 6000 [34, 35, 61]*:*

Synonym:

Carbowax; *Carbowax Sentry*; *Lipoxol*; *Lutrol E*; PEG; *Pluriol E*; polyoxyethylene glycol, Macrogol 6000.

Description:

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

Functional category:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Solubility:

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Melting point:

55–63°C

Stability and storage condition:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols should be stored in well-closed

containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Incompatibilities:

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents. The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Safety:

Generally, they are regarded as nontoxic and nonirritant materials. Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically up to 4 lit. of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.

Application:

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.

In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.

TRI ETHYL CITRATE [34, 35, 61]:

Non proprietary Names:

BP : Triethylcitrate, PHEUR : Triethylis citras, USPNF : Triethyl citrate.

Synonyms:

Citric acid,Ethyl ester,Citroflex 2,Citrofol AI,E 1505, Hydrogen CAT, TEC. ***Chemical Name:***

2-Hydroxy-1,2,3-propanetricarboxylic acid,Triethyl ester.

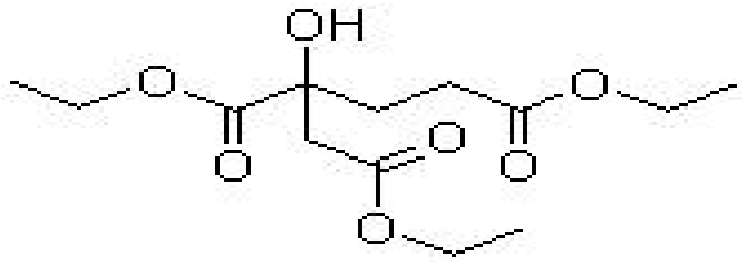
Empirical formula:

$C_{12}H_{20}O_7$.

Molecular Weight:

276.29.

Structural formula:



Category:

Plasticizer

Applications:

Used to plasticize polymers in pharmaceutical coatings. The coating applications include capsules, tablet, sustained release dosage form.

Description:

Clear,Odorless,Practically colorless,Oily liquid.

Acid value:

0.02

Boiling Point:

288˚c

Flash point:

155˚c

Solubility:

Soluble 1 in 125 of peanut oil, 1 in 15 of water.Miscible with ethanol (95 %),acetone,and propan-2-ol.

Viscosity (dynamic):

35.2 mPa s (35.2 Cp) at 25˚c.

Stability and Storage:

Stored in a closed container in a cool, dry location. When Stored in accordance with these conditions, triethyl citrate is a stable product.

Incompatibilities:

Incompatible with strong alkalis and oxidizing materials.

POLYSORBATE 80 [33, 34]:

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

SODIUM LAURYL SULPHATE [33, 34]:

Sodium lauryl sulfate is an anionic surfactant employed wide range of nonparenteral pharmaceutical formulations and cosmetics; It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins; and sodium lauryl sulfate

has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC). Ineffective against many Gram-negative microorganisms.

DISODIUM HYDROGEN PHOSPHATE [33, 34]:

Dibasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, dibasic sodium phosphate is used as a mild laxative and in the treatment of hypophosphatemia. Dibasic sodium phosphate is also used in food products; for example as an emulsifier in processed cheese.

Chapter-6

Materials and Methods

6. MATERIALS AND METHODS

6.1. LIST OF MATERIALS:

Table No.3: List of Chemicals Used

Sr. No	NAME OF MATERIAL	MANUFACTURING COMPANY
1	Lansoprazole	Enal Drugs Ltd. Hyderabad
2	Sugar spheres (600-800micron)	Sanmour pharma pvt.ltd, Mumbai
3	Di-sodium hydrogen orthophosphate	S.D fine chemicles,pvt.itd Mumbai
4	Hydroxy propyl methyl cellulose E 5	Himedia laboratories, pvt. Ltd. Mumbai
5	Talcum	Loba chemie, pvt. Ltd. Mumbai
6	Polyethylene Glycol 6000	Himedia laboratories, pvt. Ltd. Mumbai
7	Sodium lauryl sulphate	S.D fine chemicles,pvt.ltd. Mumbai
8	Eudragit L-30 D 55	Sanmour pharma pvt.ltd. Mumbai
9	Triethyl citrate	Loba chemie, pvt. Ltd. Mumbai
10	Polysorbate 80	Himedia laboratories, pvt. Ltd. Mumbai

6.2. LIST OF EQUIPMENTS:

Table No.4: Instruments Used for Formulation Development

PROCESS	EQUIPMENT	MANUFACTURER	MODEL NO.
Weighing	Electronic single pan balance	Shimadzu	BL-204
Sieving process	Mechanical sifter with sieve ≠24,30,50,60,80 and 100	Retsec	ASL 00
Density	Tapped density tester USP	Electrolab	ETD-1020
Blending	Blender	Rimek	410 AG
Stirring	Mechanical stirrer	Remi motors Bombay	RQG- 129 D
Drying	Fluidized bed dryer	Retch	TG 100
PH	PH meter	Elico India	--
Dissolution	Dissolution test apparatus USP	Lab India	--
Absorbance	UV	Lab India	UV- 1800
Peak Area	HPLC	Waters	Waters 2965
IR Spectrum	FTIR	Germany	Bruker optic GMBH

6.3. PREFORMULATION STUDIES [35, 64]:

To formulate an ideal formulation, the pre-formulation studies are usually the quantitative assessment of chemical stability of drug as well as stability in presence of other excipients for a formulation.

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study.

The following preformulation studies were performed:

- Solubility analysis
- Bulk density
- Tapped density
- Melting point
- Loss on drying
- Identification of drug- excipient compatibility

6.3.1. SOLUBILITY ANALYSIS [35]:

Solubility is important pre-formulation parameter because it affects the dissolution and bio availability of drug.

Method:

Appropriate quantity of drug was weighed and added to the suitable volume of solvent like hexane, ethanol, and water.

6.3.2. MELTING POINT [35]:

The melting point of lansoprazole was determined by capillary method, using small quantity of lansoprazole was taken and placed in apparatus and determined the melting point and matched with standards.

6.3.3. BULK DENSITY [35, 48]:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density will increase. In addition as the granule size increases bulk density decreases.

Method

A given quantity of the powder was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume is obtained. This volume is bulk volume and it includes the true volume of the powder and the void space among the powder particles.

Bulk Density **=** Bulk Mass / Bulk Volume

6.3.4. TAPPED DENSITY [35, 48]:

Tapped density was determined by using Electrolab density tester, which consists of a graduated cylinder. An accurately weighed 5gm sample of powder was carefully added to the cylinder with the aid of a funnel. The initial volume was noted, and the sample was then tapped (500,750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference was not more than 2% a sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density is calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

6.3.5. LOSS ON DRYING [35, 48]:

Determined on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Accurately weighed the substance to be tested. If the sample is in the form of large crystals, reduced the particle size to about 2 mm by quickly crushing. Tared a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in bottle, replaced the cover, and accurately weighed the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature from constant weighed. Upon opening the chamber, closed the bottle promptly, and allowed it to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where,

W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

6.3.6. COMPATIBILITY STUDY [64]:

Drug- excipient compatibility studies:

IR spectra of drug, drug and polymers and excipients were obtained by using Bruker optic GMBH FTIR spectrometer.

Method:

FTIR spectra of pure drug, and its physical mixture were obtained by using KBr pellets methods. About 2% (w/w) of samples was mixed with potassium bromide (KBr) disc. Each disc was scanned at a resolution of 4 cm^{-1} over a wave number region of 400–4000 cm^{-1} by a FTIR spectrometer.

6.3.7. CONSTRUCTION OF STANDARD CURVE [64]:

Lansoprazole (100 mg) was accurately weighed and dissolved in 100 ml methanol to form a stock solution (1000 µg/ml). The stock solution was further diluted suitably to get a working standard solution of concentration 100 µg/ml. This working standard solution was suitably diluted to give a concentration of 20 µg/ml and this was then scanned in UV range. This showed an absorption maximum at 281 nm. Aliquots (0.5,1.0,1.5,2.0 and 2.5) ml of working standard solution (100 µg/ml) corresponding to 5-25 µg were taken in a series of 10 ml volumetric flask and volume made up with water. The absorbance measurements of these solutions were carried out against methanol as blank at 281 nm. A calibration curve of lansoprazole was plotted. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

6.4. FORMULATION OF LANSOPRAZOLE PELLETS [33, 34, 59, 61]*:*

6.4.1. Different batches of pellets (F1 to F9) were formulated using the ingredient given in the

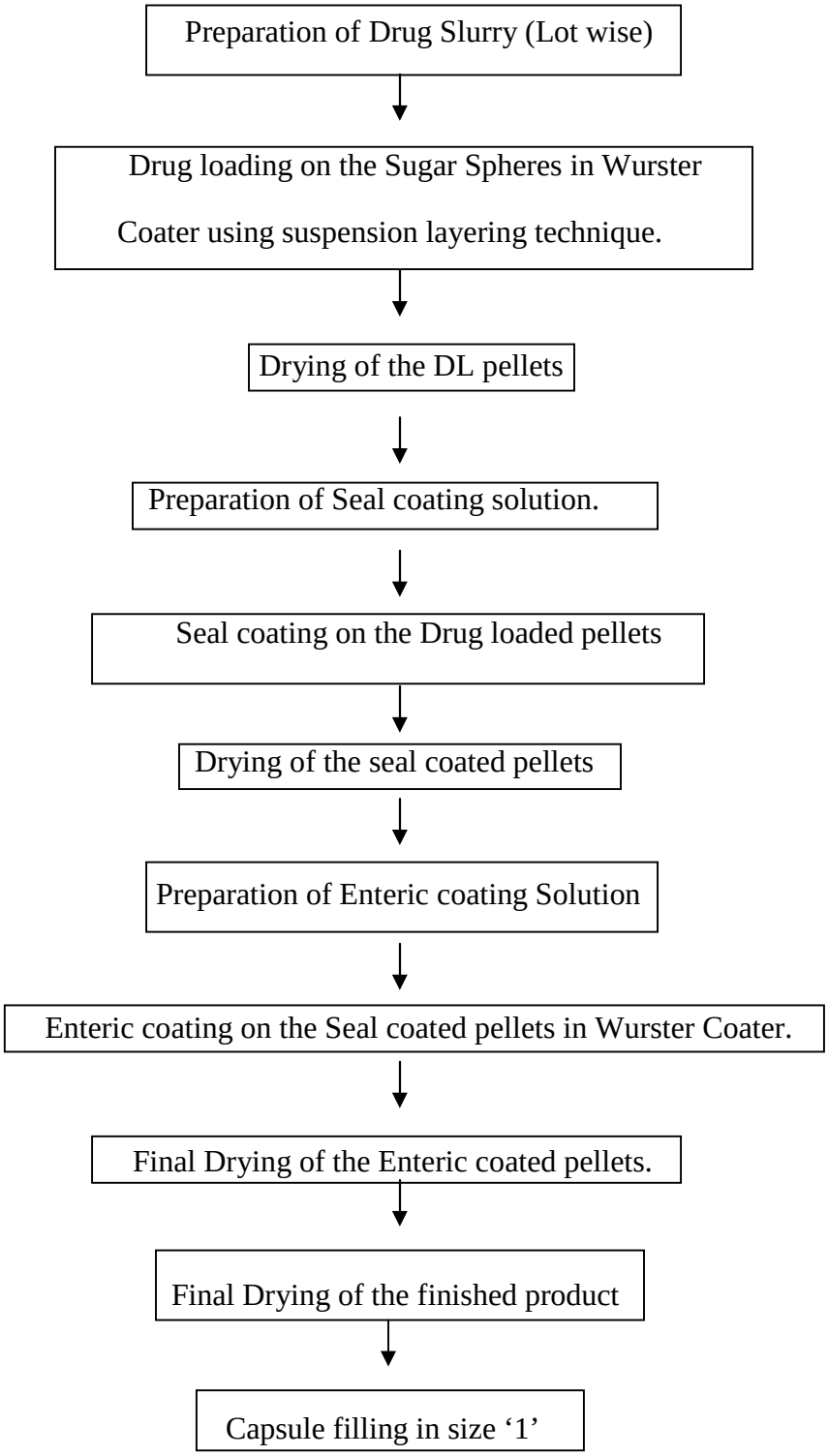
Table no.5: Formula for lansoprazole pellets:

Batch no.		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sr.no.	**Ingredients**	**mg/unit**	**mg/ unit**	**mg/unit**	**mg/unit**	**mg/unit**	**mg/unit**	**mg/ unit**	**mg/unit**	**mg/unit**
A	**DRUG LAYERING**									
1	Sugar Spheres (600-800 micron)	135.5	140.5	145.5	150.5	155.5	160.5	165.5	170.5	175.5
2	Lansoprazole, Usp (Micronized)	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
3	Di-sodium hydrogen Orthophosphate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
4	Hydroxy Propyl Methyl Cellulose E 5	20	20	25	25	30	30	35	40	40
5	Talcum Powder	10	10	10	10	10	10	10	10	10
6	Polyethylene Glycol 6000	6	6	6	6	6	6	6	6	6
7	Sodium lauryl sulphate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
8	Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
	Total	225	230	240	245	255	260	270	280	285

B	SEAL COATING OF LANSOPRAZOLE PELLETS	F1	F2	F3	F4	F5	F6	F7	F8	F9
9	Lansoprazole layered pellets	225	230	240	245	255	260	270	280	285
10	Hydroxy Propyl Methyl Cellulose E 5	20	20	25	25	30	30	35	40	40
11	Polyethylene Glycol – 6000	6	6	6	6	6	6	6	6	6
12	Talc, USP	10	10	10	10	10	10	10	10	10
13	Di-sodium hydrogen orthophosphate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
14	Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
	Total	264	269	284	289	304	309	324	339	344

C	ENTERIC COATING OF LANSOPRAZOLE PELLETES									
15	Eudragit L-30 D 55	70.00	65.00	60.00	55.00	50.00	45.00	40.00	35.00	30.00
16	Triethyl citrate, NF	9.25	9.25	9.25	9.25	9.25	9.25	9.25	9.25	9.25
17	Talc, USP	12	12	12	12	12	12	12	12	12
18	Polysorbate 80, NF	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
19	Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
	Total	359	359	369	369	378.75	379	389	399	399

Figure no.17: Process Flow chart



6.4.2. MANUFACTURING STEPS [7, 8, 9, 67, 69, 70]:

STAGE-I: Drug Loading

Preparation of drug loading solution:

Lot wise preparation method

1. Took weighed 1/3rd of the total quantity of dematerialized water in stainless steel vessel and heat the water up to 80-85ºC.
2. Sodium lauryl sulphate, poly-ethylene glycol 6000, di-sodium hydrogen phosphate was weighed and added one by one in the water and dissolved.
3. Hydroxyl propyl methyl cellulose was weighed and transferred in hot purified water under stirring and slurry of HPMC was prepared.
4. Remaining quantity of dematerialized water was added in the hot slurry under stirring to dissolve HPMC.
5. Cooled the solution up to room temperature under stirring.
6. Checked pH and adjusted pH to 9.0 (Acceptable Range 8.5 – 9.5) if necessary by adding more buffer.
7. Lansoprazole USP was weighed and added in above solution slowly under stirring; stirred until uniform slurry to be formed.
8. Then purified talcum was added under stirring.
9. Finally mixed properly for 10 minutes, and passed solution through 100 meshes. Stored the solution in a well closed container.

In process check:

Table No.6: FBC Parameters

Inlet temp	60ºC
Bed temp	40ºC
Atomizing air pressure	2 bar
Spray Rate	15 ml/min

Drug loading Process

Equipment Used: - Fluid Bed Processor with Wurster facility (bottom spray).

Process parameters are as follows:-

Inlet Air Temperature	:	60º C
Product Bed Temperature	:	47ºC – 50ºC
Outlet Temperature	:	43ºC – 46ºC
Nozzle Diameter	:	1.0 mm
Atomization Air Pressure	:	2.2 – 2.5 Bar
Spray Rate	:	5 gms / min
Final Drying time	:	30 mins.

Coated pellets are collected in double polythene lined containers.

STAGE-II: Seal Coating

Preparation method:

1. Took weighed 1/3rd of quantity of dematerialized water in stainless steel vessel and heat the water up to 80-85^{0}C.
2. Poly-ethylene glycol 6000, hydroxyl propyl methyl cellulose was weighed and added one by one in the water and dissolved.
3. Remaining quantity of purified water was added to the above solution under stirring.
4. Cooled the solution up to room temp under stirring.
5. Purified talcum was added under stirring.
6. Then di-sodium hydrogen orthophosphate was weighed and added under stirring.
7. Finally mixed for 10 minutes, and pass the solution through 100 meshes. Stored the solution in a well closed container.

8. ***SEAL COATING OPERATIONS***

Process parameters are as follows:-

Inlet Air Temperature	:	60º C
Product Bed Temperature	:	44ºC – 47ºC
Outlet Temperature	:	40ºC – 43ºC
Nozzle Diameter	:	1.0 mm
Atomization Air Pressure	:	2.2 – 2.5 Bar
Spray Rate	:	6 gms / min
Final Drying time	:	30 mins

Coated Pellets are collected in double polythene lined container.

STAGE-III: Enteric coating

Preparation of coating solution:

1. Purified water was taken in a stainless steel vessel.
2. Triethyl citrate, polysorbate 80 was weighed and added one by one in the above mentioned water and dissolved.
3. Purified talcum was weighed and added under stirring.
4. Eudragit L 30 D55 was weighed and adde to the above solution under mild stirring. An ordinary propeller stirrer suffices. Continue stirring for another 15-20 mins.
5. Filtered the final dispersion through 100 mesh screen only.
6. The dispersion was now ready for use.
7. The dispersion was kept under mild stirring during the coating operation.

Enteric coating process:

Perform enteric coating operations by using the following set of parameters:

Inlet Air Temperature	:	45º C
Product Bed Temperature	:	34ºC – 37ºC
Outlet Temperature	:	36ºC – 39ºC
Nozzle Diameter	:	1.0 mm
Atomization Air Pressure	:	1.5 – 2.0 Bar
Spray Rate	:	10 gms / min
Final Drying time	:	30 mins

Coated Pellets were collected in double polythene lined container.

Unloaded & weighed the pellets in double lined polythene bags in clean, tared and labeled plastic drum & closed (air tight) the bags & drums.

6.5. EVALUATION OF FORMULATED LANSOPRAZOLE PELLETS:

6.5.1. FRIABILITY [49]:

There was no standard method established for evaluating friability of pellets. The friability of pellets was determined by using Roche friabilator. But due to the low weight of the pellets the mechanical stress applied is less. This can be corrected by adding glass or steal balls to increase stress. The friability was calculated as percentage weight loss according to the following equation:-

$$\% \text{ Friability } = \frac{\text{Initial weight - Final Weight}}{\text{Initial weight}} \text{ X } 100$$

6.5.2. BULK AND TAPPED DENSITY [48]:

6.5.2.1. BULK DENSITY [48]:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density is increase. In addition as the granule size increases bulk density decreases.

Method

A given quantity of the Lansoprazole pellets was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume is obtained. This volume is bulk volume and it includes the true volume of the powder and the void space among the powder particles.

Bulk Density **=** Bulk Mass / Bulk Volume

6.5.2.2. TAPPED DENSITY [48]:

Tapped density was determined by using Electrolab density tester, which consists of a graduated cylinder. An accurately weighed 5gm sample of pellets was carefully added to the cylinder with the aid of a funnel. The initial volume was noted, and the sample was then tapped (500,750 or 1250 tapping) until no further reduction in volume was noted or the percentage of difference is not more than 2%.A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density was calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

6.5.3. *HAUSNER'S RATIO* [48]:

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

$$\textbf{Hausner's ratio} = v_i / v_t$$

Where v_t = Tapped volume

v_i = untapped volume

Limits:

Table no.7: limits of Hausner's ratio value

S.No	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.5.4. *ANGLE OF REPOSE* [35, 48, 49]:

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by allowing the pellets to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height. The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

$$\theta = \tan^{-1}(h/r)$$

Where, θ= angle of repose

h= height of the heap

r = radius of the base of the heap

Table no. 8: limits of angle repose value

Angle of Repose (Degrees)	Type of Flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very Poor

6.5.5. PARTICLE SIZE DETERMINATION [42, 45, 51]:

In order to determine the particle size distributions of the prepared pellets containing lansoprazole, standard sieve method was used. Mechanical sifter with sieves between apertures 355-2000 µm were used by using all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

6.5.6. ASSAY STUDY [71]:

Chromatographic condition

Column: 4.6mm ID x 25cm long. Packaged with C18 with particle size 5µ.

Flow Rate: 1.0 ml/min.

Wave length: 285 nm

Buffer PH: Dissolved 6.8 gm of potassium dihydrogen orthophosphate in 1000ml water. Adjusted PH 7.4 with 0.1 M sodium hydroxide.

Mobile Phase: Prepared a suitable quantity of a filtered and degassed mixture of 65 volumes of phosphate buffer PH 7.4 and 35 volumes of acetonitrile.

Standard preparation:

Lansoprazole pellets (10 mg.) was weighed accurately and transferred into a 100 ml volumetric flask. 40 ml of 0.1 M Sodium hydroxide was added and sonicated to dissolve. Made volume up to the mark with 0.1 M sodium hydroxide and mixed. Transferred 5 ml of the solution to 50 ml with mobile phase and mixed.

Sample Preparation*:*

Took around 5 gms of pellets into a mortar and pestle and grinded the pellets into a uniform fine powder. Weighed accurately about a quantity equivalent to 30mg of Lansoprazole into a dry 100 ml volumetric flask, added about 50 ml of 0.1 M NaOH and sonicated to dissolve. Made volume up to the mark with 0.1 M sodium hydroxide and mixed. Transferred 20 to 30 ml of solution into dry stopper test-tube, centrifuge at 5000 rpm for 5 minutes. Further, diluted 5 ml of the supernatant solution to 50 ml with mobile phase.

Procedure:

Injected sample preparation in duplicate into the chromatograph and recorded the chromatograms. Measured the response for the major peaks. Calculated the quantity in % w/w of Lansoprazole by using below formula.

$$\text{Calculation: } \frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{50} \times \frac{100}{WT} \times \frac{50}{5} \times P$$

AT= Average peak area of sample preparation

AS = Average peak area of standard replicate injection

WS = Weight of working standard in mg

WT = Weight of sample taken in mg

P = Purity of working standard

6.5.7. GASTRIC ACID RESISTANT TEST [41, 55]:

Acid resistance test is a significant index of drug dissolution performance of enteric coated formulations. Model fraction of coated pellets was subjected for acid resistance test in USP dissolution test apparatus –II (SR-8, Hanson Research, and Chatsworth, USA). Weighed amount of pellets were placed in the vessel and test was carried out in 0.1N HCl for 1hr at 75 rpm. Lansoprazole released at 1hr in 0.1 N HCl was estimated as per method specified in USP. Minimal amount of drug release in this test is indicative of gastric acid resistance.

6.5.8. INVITRO DISSOLUTION STUDY [40, 41, 55, 56]:

Method:

Dissolution studies were carried out for all the formulations, employing USP-II paddle method 500 ml of 0.1 N HCL for first 1 hr and 900 ml of phosphate buffer pH-6.8 for next 1 hr were used as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Pellets were placed in the vessel and the vessel was covered and operated for 1 hr in 0.1 N HCL at 75 rpm and next 1 hr pH-6.8 phosphate buffer at 100 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 281 nm using UV-spectrophotometer.

Preparation 0f 0.1 N HCL:

Transferred 8.5 ml of HCL into a suitable container containing water, dilute to 10,000 ml with purified water and mixed.

Dissolution Parameters

Medium	: 0.1 N HCL
Volume	: 500 ml
Apparatus	: USP type II (paddle)
Speed	: 75 RPM
Temperature	: 37.0˚c ± 0.5˚c
Sampling point	: 15, 30, 45 and 60 min.

Preparation of buffer:

Weighed and transferred 1.41 grams of disodium hydrogen phosphate anhydrous into a beaker containing 1000 ml of water. Filtered through 0.45µ membrane filter.

Dissolution Parameters:

Medium	: PH 6.8 phosphate buffer
Volume	: 900ml
Apparatus	: USP type II (paddle)
Speed	: 100 RPM
Temperature	: 37.0˚c± 0.5˚c
Sampling points	: 75, 90,105 and 120 min

6.5.9. SCANNING ELECTRON MICROSCOPY [45, 46]:

Photo micro graphs were taken with a scanning electron microscope for visualization of spherocity of the pellets. Pellets were coated with platinum by means of a sputter coater to assure conductivity.

6.5.10. COMPARISON OF DISSOLUTION PROFILE OF OPTIMIZED FORMULATION WITH MARKETED FORMULATION [40, 41, 55, 56]:

Invitro study of marketed formulation was carried out according to the procedure given in section 6.5.8. Graph of cumulative percentage drug release Vs time (hour) for both the optimized formulation and marketed product was plotted.

6.5.11. ACCELERATED *STABILITY STUDY [40, 41, 55]:*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retesting for the drug substance or a shelf-life for the drug product and recommended storage conditions.

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product.ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use.

The ICH Guidelines have established that accelerated stability testing should be done at 40^0C/75%RH for 3 months.

Stability study was carried out for the optimized formulation. Tablets of optimized formulation were packed in strip and kept in stability chamber for 3 months on above mention temperature. Samples were analyzed at 1, 2, 3 months for *invitro* dissolution study.

ICH guidelines for stability study

Table no.9: ICH guidelines

Study	Storage condition	Time period
Long term*	25°c±2°c/60% RH±5% RH or 30°c±2°c/65% RH±5% RH	12 month
Intermediate**	30°c±2°c/65% RH±5% RH	6 month
Accelerated	40°c±2°c/75% RH±5% RH	6 month

Chapter-7

Results and Discussion

7. RESULTS AND DISCUSSION

7.1. *PREFORMULATION STUDIES:*

7.1.1. SOLUBILITY:

Sparingly soluble in ethanol and insoluble in water and hexane

7.1.2. MELTING POINT:

The Melting point of lansoprazole was found to be 178-182 ^{o}C

7.1.3. BULK AND TAPPED DENSITY

Table no.18: Bulk density and tapped density of lansoprazole

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
LANSOPRAZOLE	0.90	1.10

7.1.4. *LOSS ON DRYING:*

LOD of lansoprazole was found to be 0.39% w/w (not more than2 % w/w)

7.1.5. COMPATIBILITY STUDIES:

FTIR spectrum of lansoprasole and physical mixture of lansoprasole and excipient were obtained according to procedure given in section 6.3.6. and results given in fig. no.19 to fig. no. 22 and characteristics peak values given in table no.10.

Figure no.19: FTIR Spectra of lansoprazole

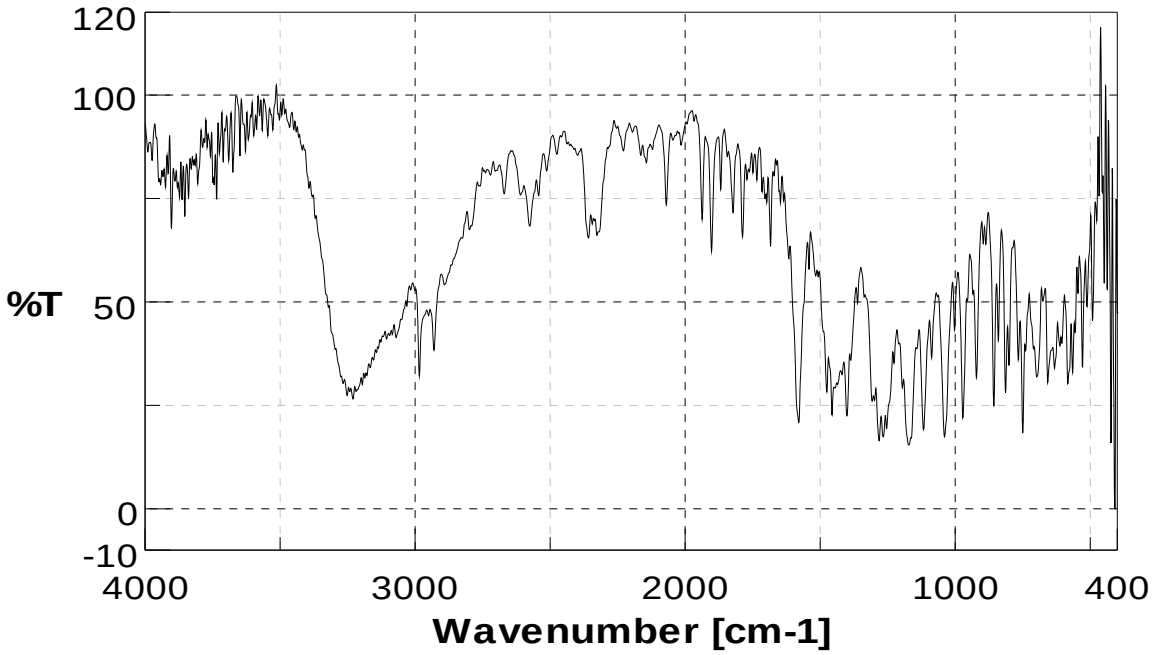


Figure no.20: FTIR Spectra of lansoprazole with HMPC E5

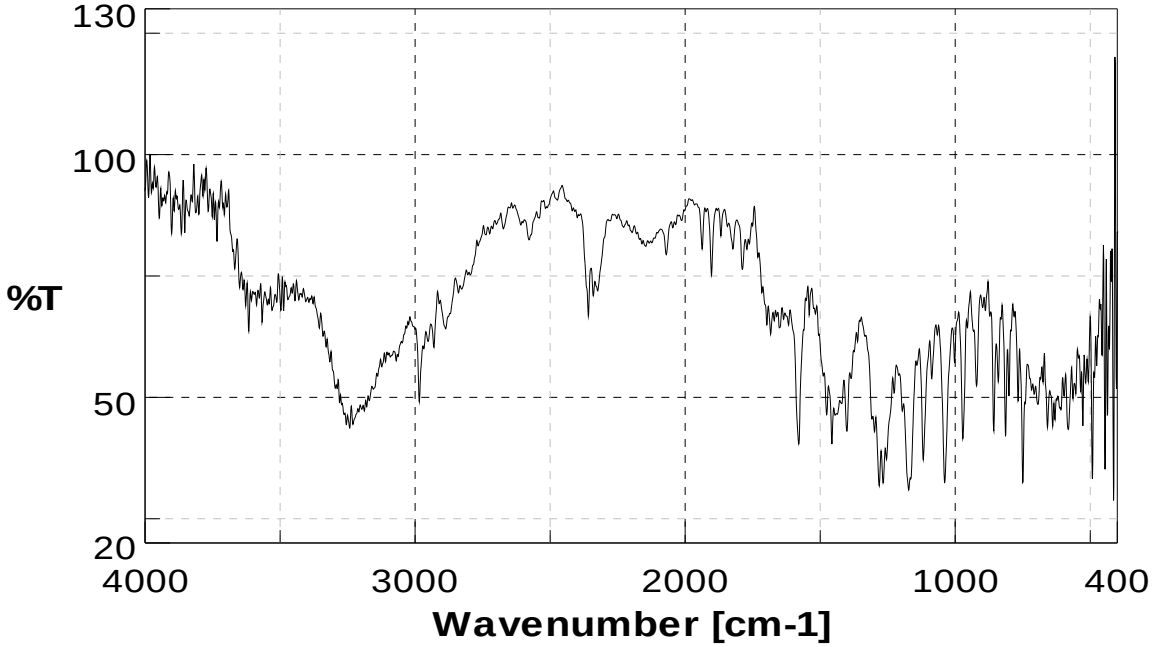


Figure no.21: FTIR Spectra of lansoprazole with Eudragit L30 D55

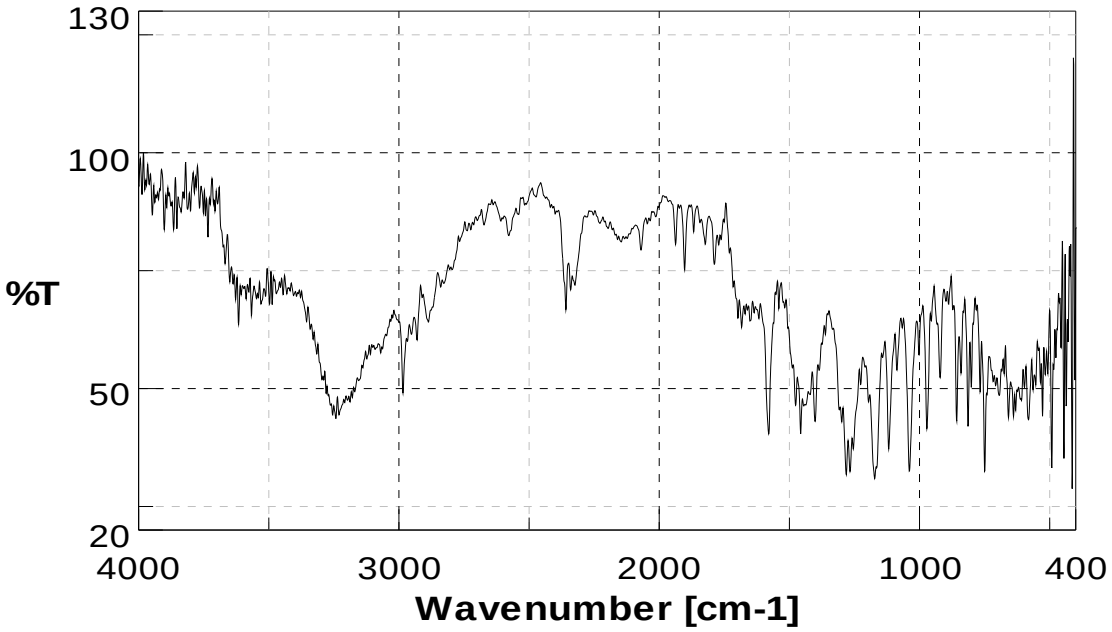
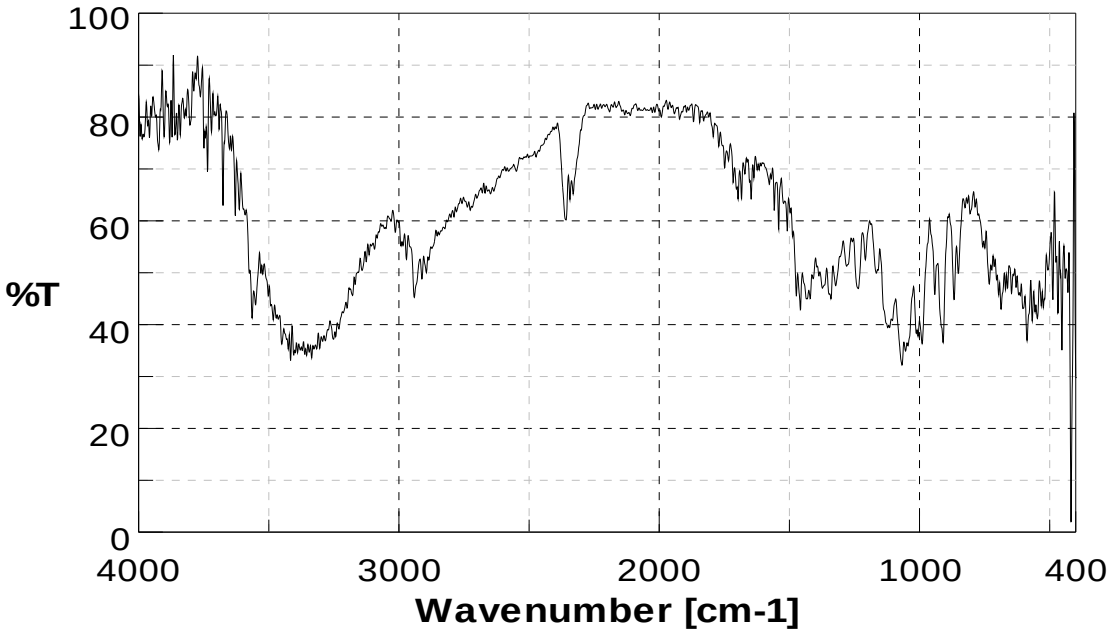


Figure no.22: FTIR Spectra of lansoprazole pellets



The IR Spectroscopy study showed following characteristic peaks of functional groups in lansoprazole.

Table No.10: IR Interpretation of Lansoprazole Drug

Sr. no.	Functional Groups	Theoretical value in cm^{-1}	Observed value in cm^{-1}
1	N-H	1306,1275	1281.47
2	N=N & C=C	1600-1430	1455.99
3	C-F	1400-1000	1401.03
4	Pyridine Ring	1600-1430	1579.47

The Lansoprazole showed characteristic peaks at 1306, 1275 (N-H), 1600-1430 (N=N, C=C), 1400-1000 (C-F) and pyridine ring peak at 1600-1430 cm^{-1}. The FTIR study showed that selected polymers were compatible with drug as all characteristic peaks of Lansoprazole were present in physical mixture of drug and polymer. Hence further formulations were prepared and evaluated for optimization of the formulation.

From the IR spectroscopy it was clear that the Lansoprazole was compatible with the polymer used Eudragit L30 D55 and HPMC E- 5.

Table No.11: Drug - Excipient Compatibility Studies

Sr. No.	Name of ingredient	Category	Remarks
1	HPMC E- 5	Film former	Compatible
2	Eudragit L30 D55	Enteric coating agent	Compatible

7.1.6. CALIBRATION CURVE OF LANSOPRAZOLE:

Calibration curve of lansoprazole was determined by plotting absorbance/concentration (mcg/ml) at 281nm, the results obtained were given in table no.12 and fig. no.16.

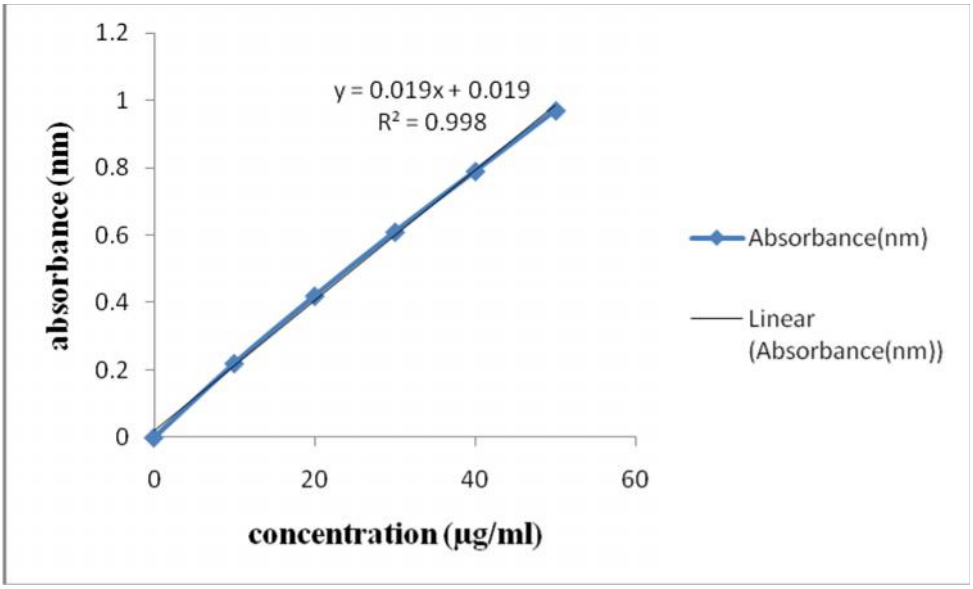
Table No.12: Standard Graph Readings (visible spectra)

Concentration (µg/ml)	Absorbance(nm)
0	0.0
10	0.220
20	0.420
30	0.610
40	0.790
50	0.970

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

$$Y = mx + c$$

Figure no.14: Standard plot of Lansoprazole



The above graph showed the standard curve of the Lansoprazole and from it correlation coefficient value was calculated as 0.998.

The above graph showed the linearity in curve and therefore it revealed that it follows the beers law.

7.2. FORMULATION OF LANSOPRASOLE PELLETS:

According to the formula and procedure given the section 6.4, pellets of all batches were formulated.

7.3. EVALUATION OF FORMULATED LANSOPRAZOLE PELLETS:

Evaluation of formulated lansoprasole pellets were carried out according to procedure given section 6.5.

7.3.1. FRIABILITY TEST:

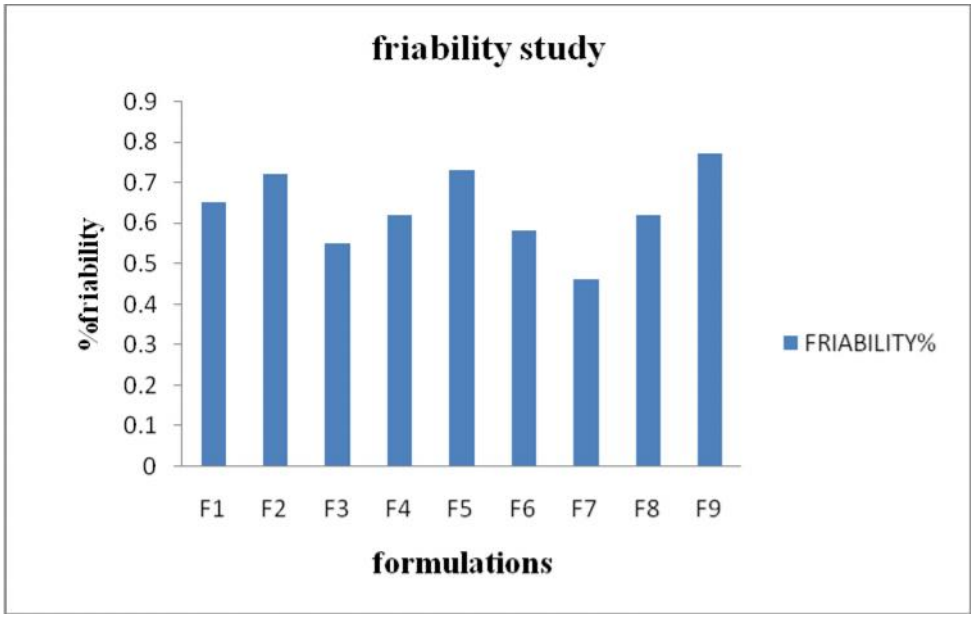
Results for friability test were given in the table no.13 and fig. no.23.

Table No. 13: percent friability of formulations F1 to F9

SR.NO.	FORMULATION	FRIABILITY%
1	F1	0.65±0.01
2	F2	0.72±0.03
3	F3	0.55±0.02
4	F4	0.62±0.07
5	F5	0.73±0.03
6	F6	0.58±0.01
7	F7	0.46±0.02
8	F8	0.62±0.03
9	F9	0.77±0.05

All values represent mean ± standard deviation (SD) n=3.

Figure no.23: percent friability of various formsulations



Above graph showed the percent friability of all formulations and it was observed that all the prepared pellets showed that percent friability value less than 1%, therefore the results were within the range.

7.3.2. BULK AND TAPPED DENSITY

Table no.14: bulk and tapped density of formulation of F1 toF9

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner Ratio	Carr's Index
F1	0.923±0.02	0.989±0.03	1.07±0.01	5.47±0.03
F2	0.937±0.03	1.0048±0.06	1.07±0.05	5.71±0.06
F3	0.921±0.02	0.988±0.02	1.07±0.04	4.38±0.07
F4	0.934±0.02	0.991±0.04	1.06v0.02	4.96±0.08
F5	0.915±0.3	0.959±0.05	1.04±0.02	5.21±0.04
F6	0.952±0.04	0.999±0.02	1.04±0.06	5.47±0.04
F7	0.947±0.01	1.028±0.04	1.08±0.07	5.39±0.06
F8	0.928±0.02	0.972±0.06	1.04±0.01	5.11±0.03
F9	0.938±0.04	0.987±0.4	1.05±0.04	4.96±008

All values represent mean ± standard deviation (SD) n=3.

The result showed in table no.14 given the the bulk and tapped density, Hausner ratio and Carr's Index for all formulation and all values were found within limit, therefore it revealed that the pellets of all formulations has good flow property.

7.3.3. ANGLE OF REPOSE:

Results for angle of repose given in table no.15.

Table No.15: angle of repose of formulations

Formulation code	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F 9
Angle of repose(degree)	27.32	26.56	28.12	28.54	29.21	27.76	29.23	27.45	28.23

All values represent mean (n) =3.

The angle of repose of formulations from F1 to F9 found between 26.56 to 29.23, so angle of repose of all formulation were below 30, therefore it was indicates that pellets were having good flow property.

7.3.4. PARTICLE SIZE DETERMINATION:

Results for particle size determination were given in the table no. 16.

Table No.16: angle of repose of formulations

Formulation code	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F8**	**F 9**
Particle size (µm)	1165.47	1128.56	1194.34	1034.23	1134.51	1098.57	1057.25	1147.78	1196.45

All values represent mean (n) =3.

From above results it was observed that the average particle sizes of the pellets were nearly 1200 µm for all 9 formulations.

7.3.5. ASSAY STUDIES

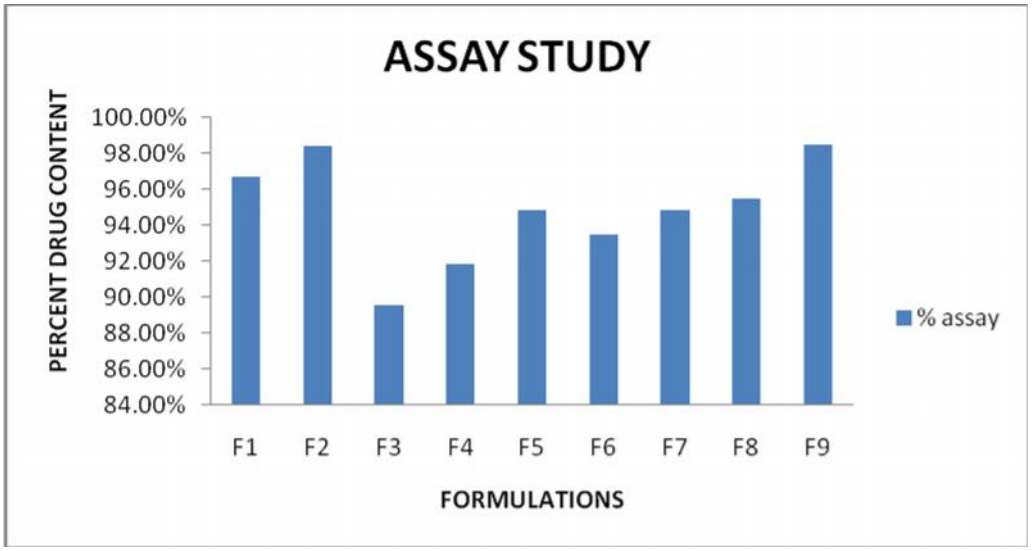
Results for assay studies were given in table no.17 and fig. no.24 to 33.

Table No.17: Assay Observation

S.NO	FORMULATIONS	%ASSAY
1	F1	96.70±0.02
2	F2	98.40±0.04
3	F3	89.60±0.03
4	F4	91.88±0.06
5	F5	94.83±0.07
6	F6	93.50±0.0.2
7	F7	94.88±0.03
8	F8	95.49±0.07
9	F9	98.50±0.04

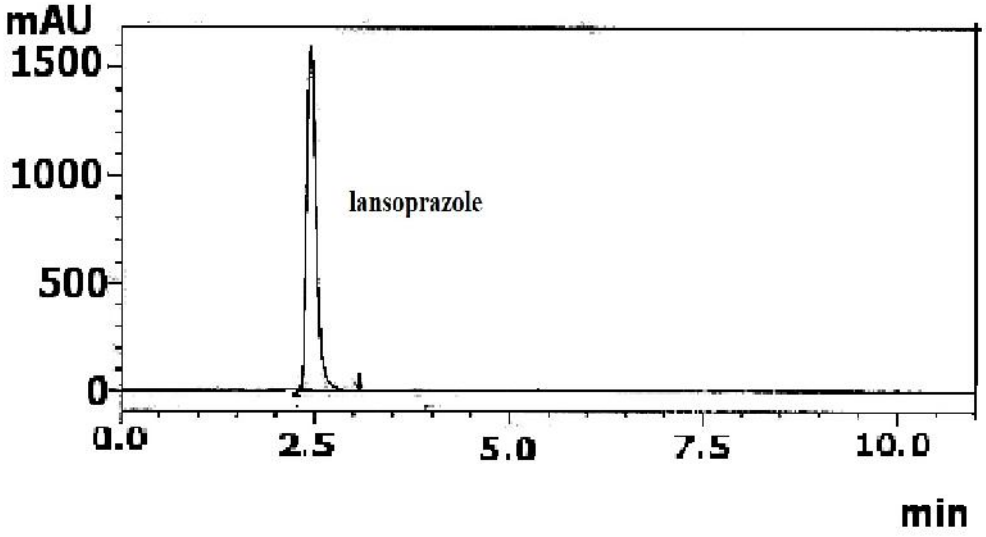
All values represent mean ± standard deviation (SD) n=3.

Figure No.24: percent assay of various formulations



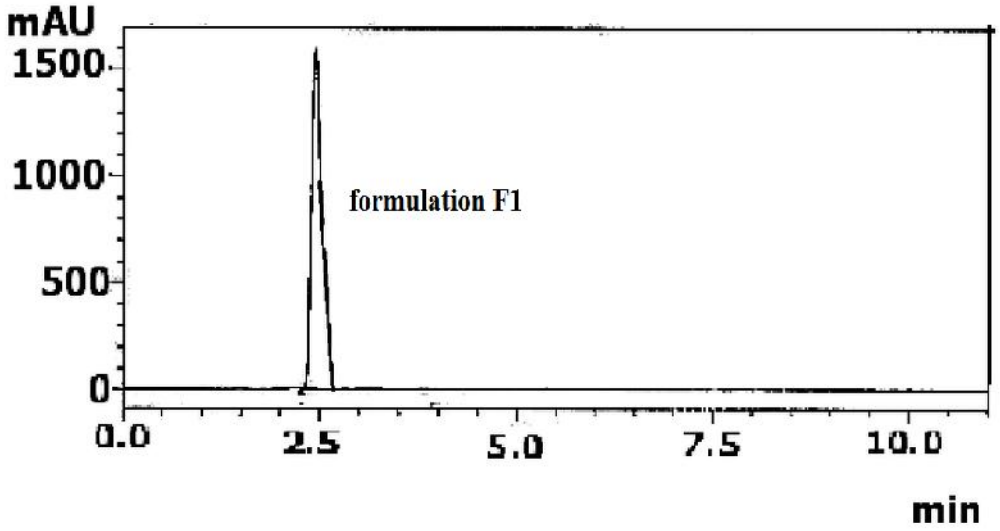
Above graph showed the percent drug content in each formulations and it was observed that the all formulations content the drug within the limit (not less than 89% and not more than 109%)

Figure no.25: Chromatogram of Lansoprazole Pure Drug



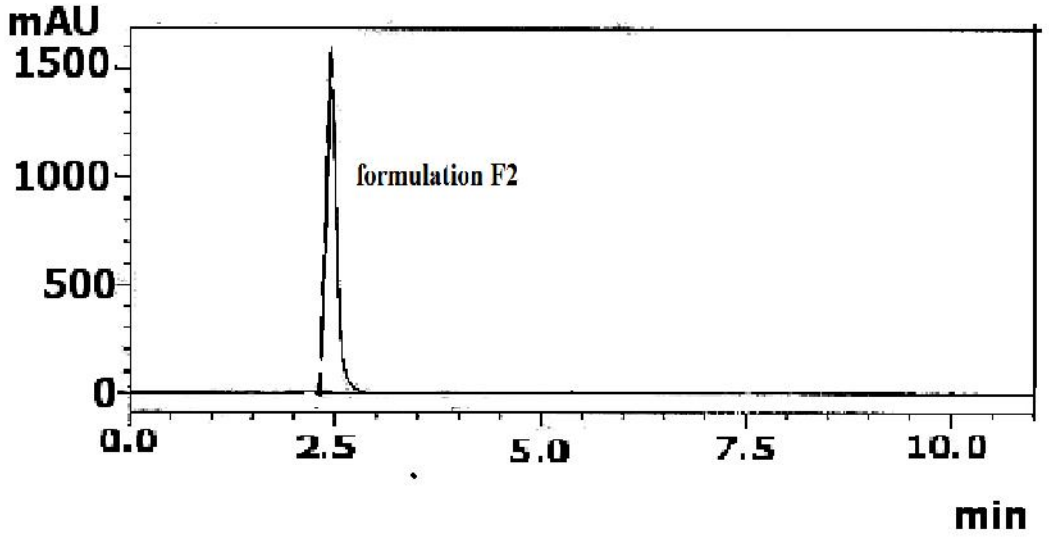
HPLC peak showing a retention time of 2.53

Figure no. 26: Chromatogram of Lansoprazole (F1 batch)



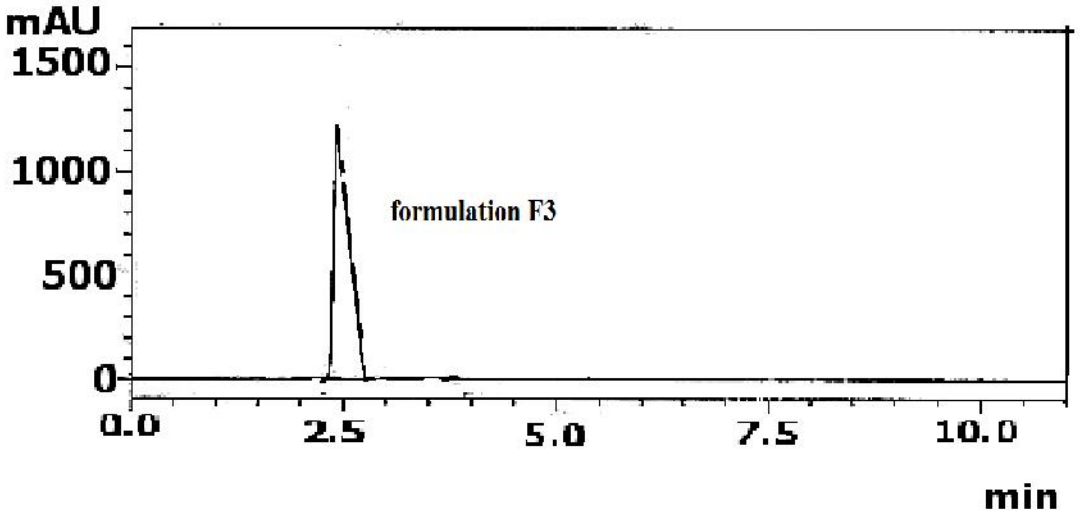
HPLC peak showing a retention time of 2.51corresponding to lansoprazole at 288nm

Figure no. 26: Chromatogram of Lansoprazole (F2 batch)



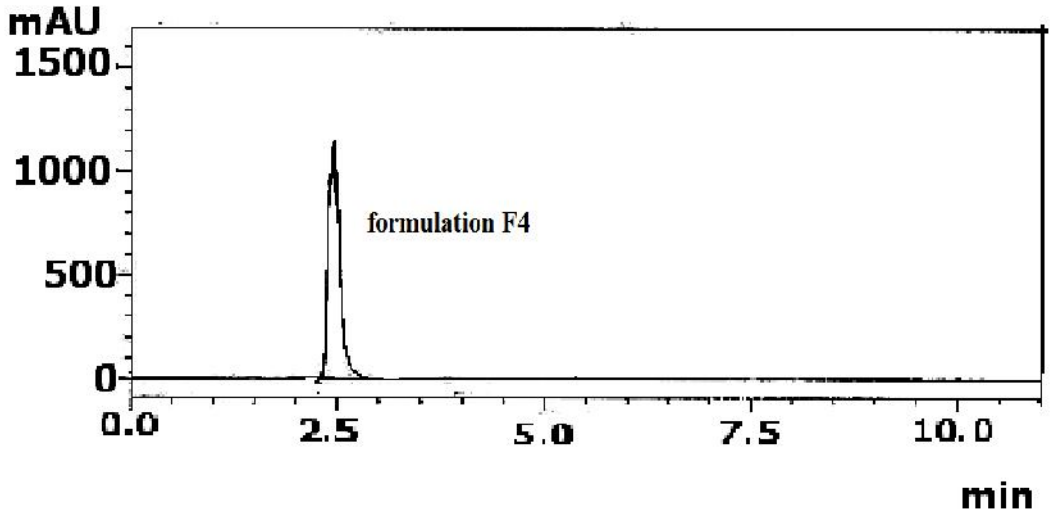
HPLC peak showing a retention time of 2.54 corresponding to lansoprazole at 288nm

Figure no. 27: Chromatogram of Lansoprazole (F3 batch)



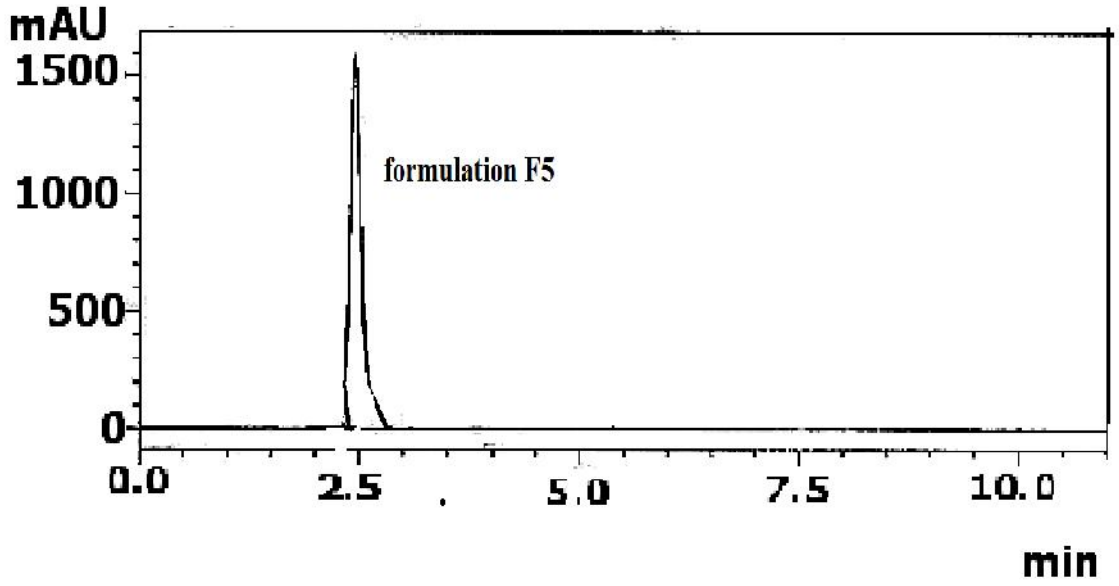
HPLC peak showing a retention time of 2.53 corresponding to lansoprazole at 288nm

Figure no. 28: Chromatogram of Lansoprazole (F4 batch)



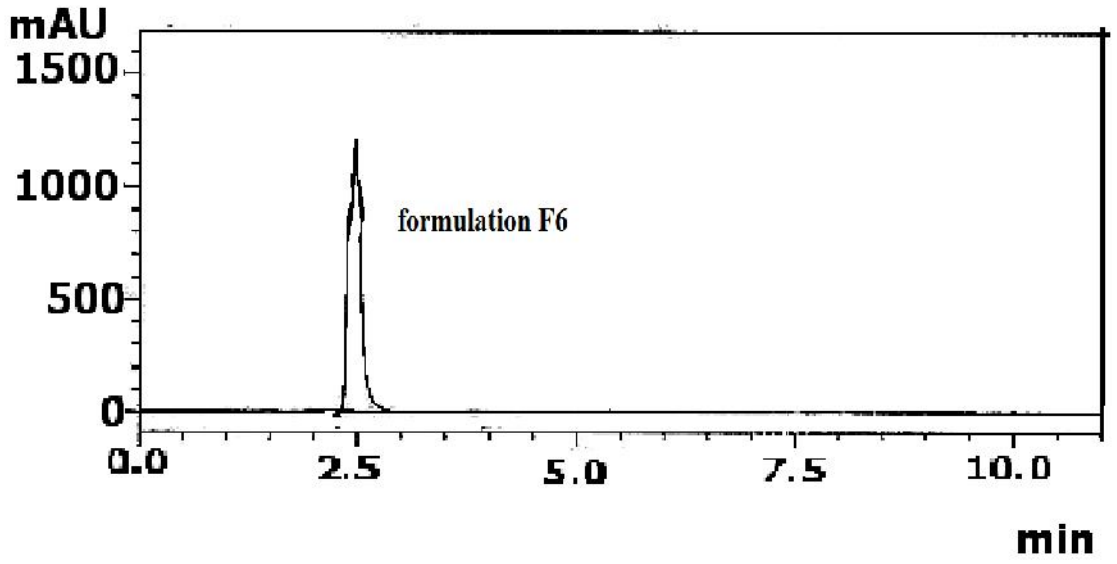
HPLC peak showing a retention time of 2.56 corresponding to lansoprazole at 288nm

Figure no. 29: Chromatogram of Lansoprazole (F5 batch)



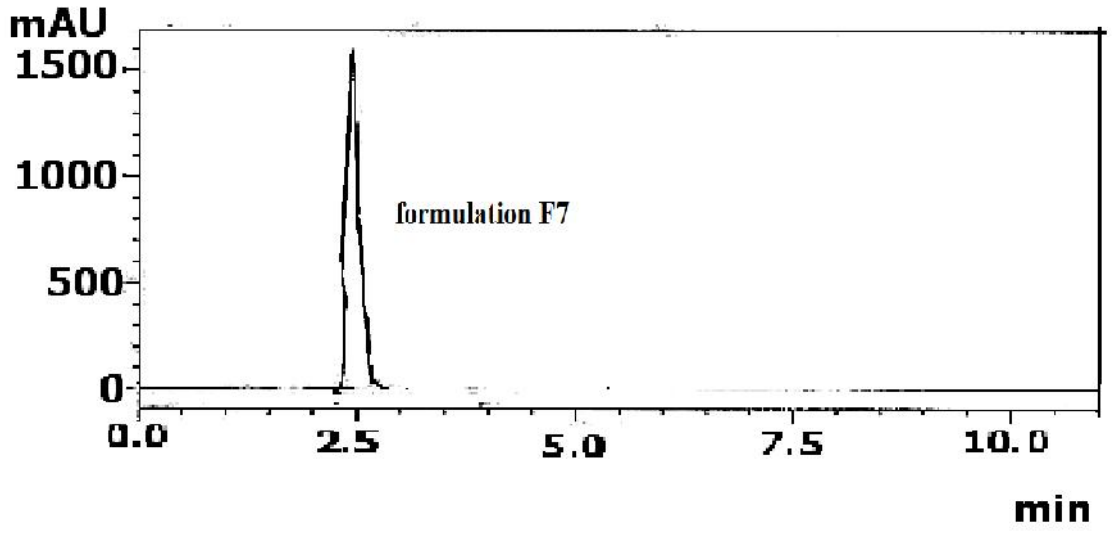
HPLC peak showing a retention time of 2.55 corresponding to lansoprazole at 288nm

Figure no. 30: Chromatogram of Lansoprazole (F6 batch)



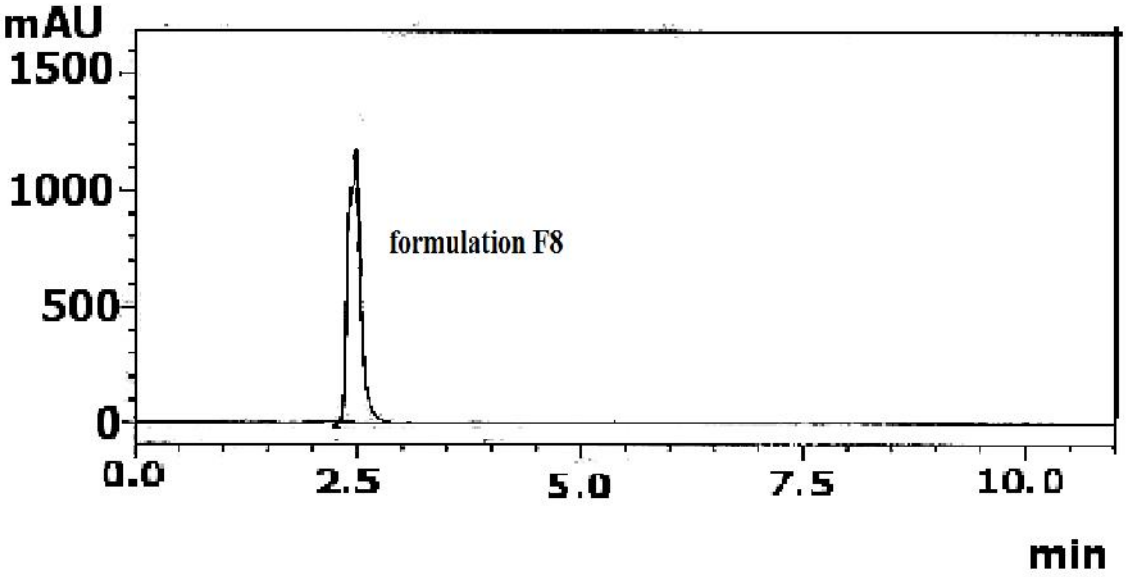
HPLC peak showing a retention time of 2.55 corresponding to lansoprazole at 288nm

Figure no. 31: Chromatogram of Lansoprazole (F7 batch)



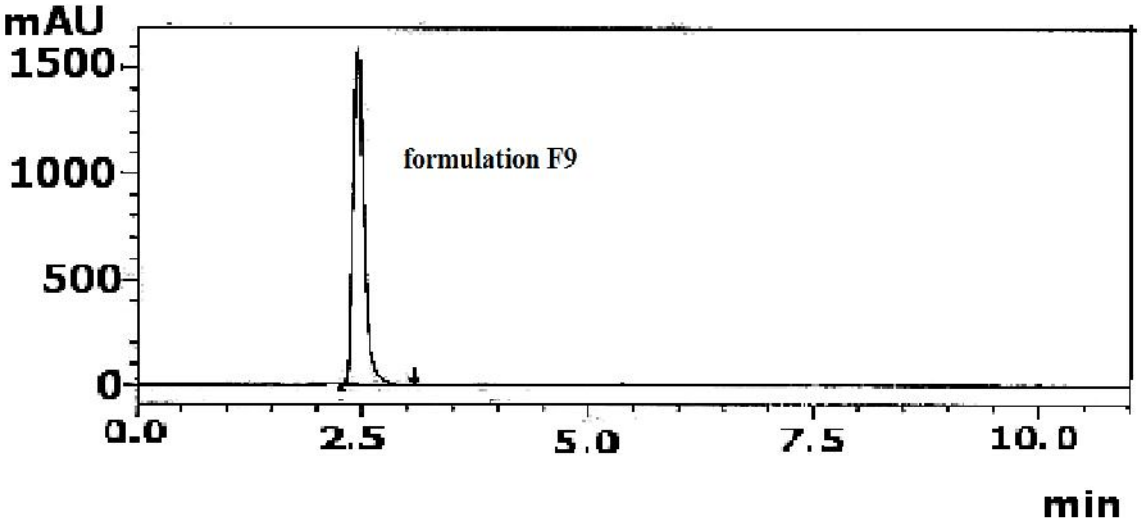
HPLC peak showing a retention time of 2.57 corresponding to lansoprazole at 288nm

Figure no. 32: Chromatogram of Lansoprazole (F8 batch)



HPLC peak showing a retention time of 2.52 corresponding to lansoprazole at 288nm

Figure no. 33: Chromatogram of Lansoprazole (F9 batch)



HPLC peak showing a retention time of 2.54 corresponding to lansoprazole at 288nm

7.3.6. GASTRIC ACID RESISTANCE TEST:

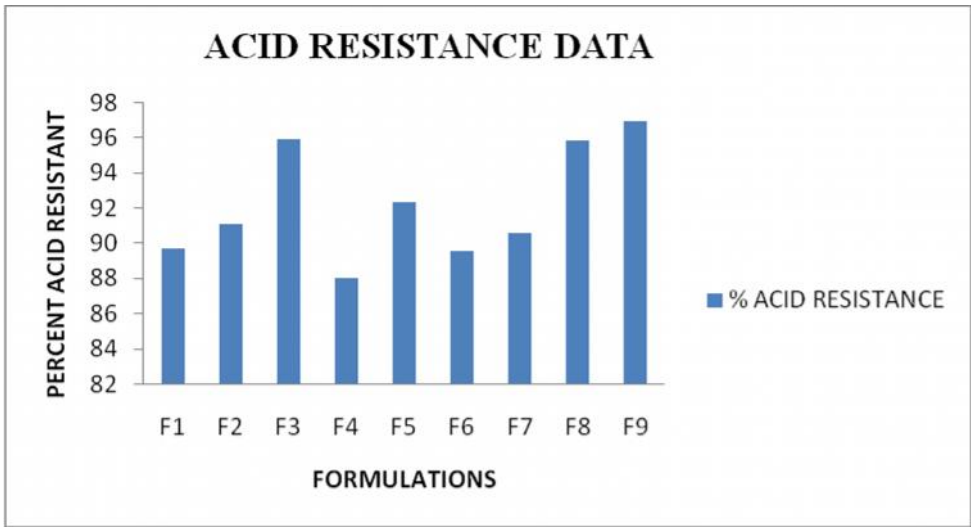
Results for the acid resistant test were given in table no.18 and fig. no.34.

Table No. 18: percent gastric resistant of formulation F1 to F9

FORMULATION	% ACID RESISTANCE
F1	89.68±0.05
F2	91.06±0.03
F3	95.87±0.07
F4	87.97±0.01
F5	92.33±0.04
F6	89.49±0.03
F7	90.56±0.02
F8	96.87±0.06
F9	95.78±0.02

All values represent mean ± standard deviation (SD) n=3.

Figure no.34: Acid resistance dissolution data



The above graph showed the percent acid resistant of all formulations and it was observed that the all formulations have better acid resistant.

7.3.7. INVITRO DISSOLUTION STUDIES:.

Results for *invitro* dissolution studies were given the table no.19 and graph for formulations F1 to F3, F4 to F6 and F7 to F9 in 0.1N HCL were showed in fig. no. 35, 36 and 37 respectively and graph for formulation F1 to F3, F4 to F6 and F7 to F9 in phosphate buffer pH 6.8 were showed in fig. no. 38, 39 and 40 respectively.

Table No.19: Cumulative percentage of lansoprazole release in 0.1N HCL and phosphate Buffer pH 6.8

	Cumulative Percent drug release in 0.1 N HCL								
TIME (MIN)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
15	0.67	0.65	0.61	0.70	0.73	0.59	0.56	0.52	0.49
30	0.72	0.69	0.65	0.72	0.66	0.62	0.60	0.58	0.57
45	0.85	0.83	0.90	0.80	0.77	0.74	0.71	0.68	0.64
60	0.91	0.87	0.85	0.83	0.96	0.81	0.79	0.76	0.71
Cumulative Percent drug release in phosphate buffer pH 6.8									
75	55.13	58.01	60.22	62.11	70.15	65.22	67.33	69.45	71.25
90	67.04	62.11	65.09	67.41	69.05	72.18	75.13	77.03	79.10
105	65.34	75.65	67.45	71.07	73.19	76.24	79.06	82.18	85..09
120	67.57	72.56	75.34	79.13	82.67	86.56	90.20	94.15	97.87

All values represent mean (n) =3.

Figure no.35: Cumulative Percentage of Release of Lansoprazole in 0.1N HCL

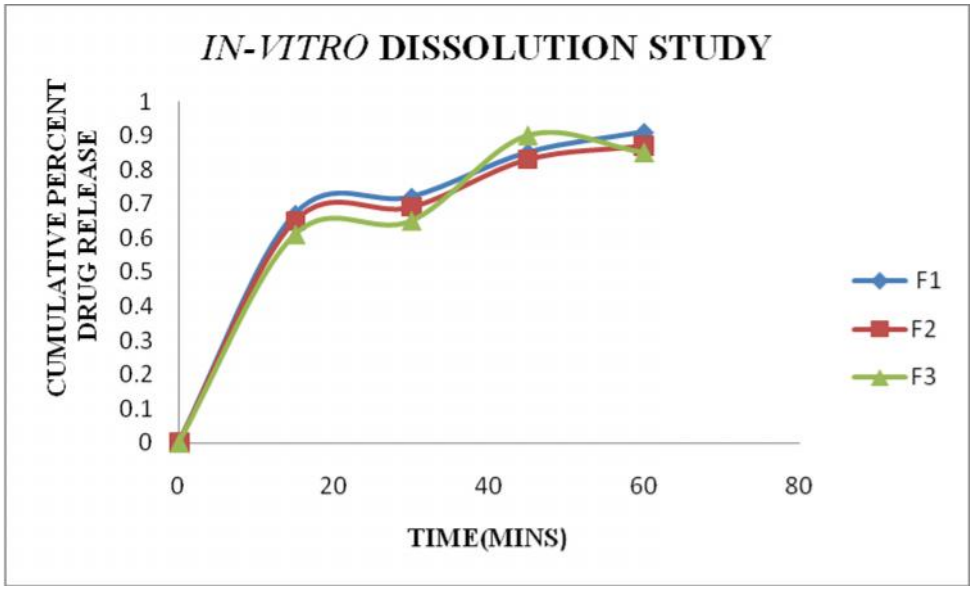


Figure no.36: Cumulative Percentage of Release of Lansoprazole in 0.1N HCL

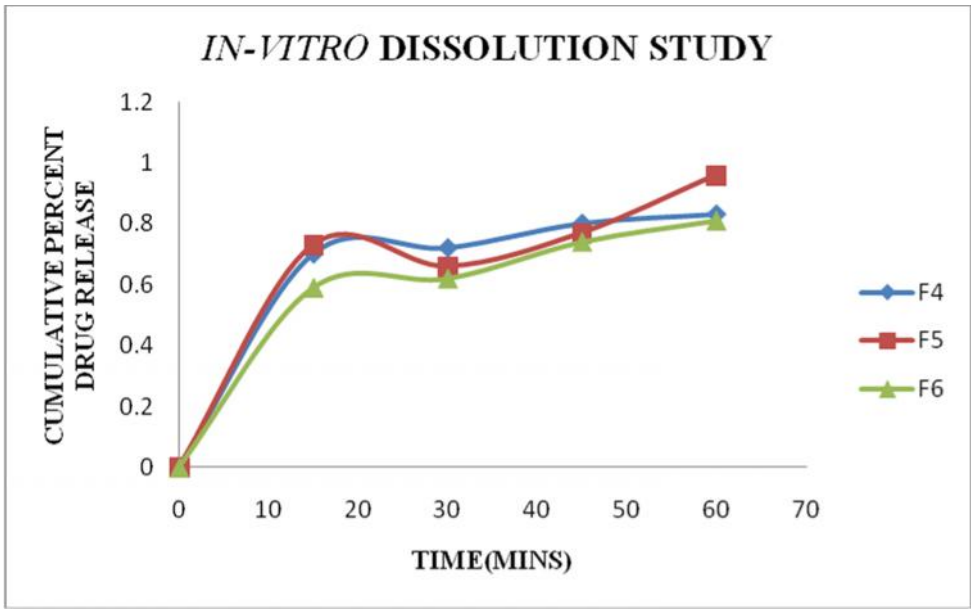
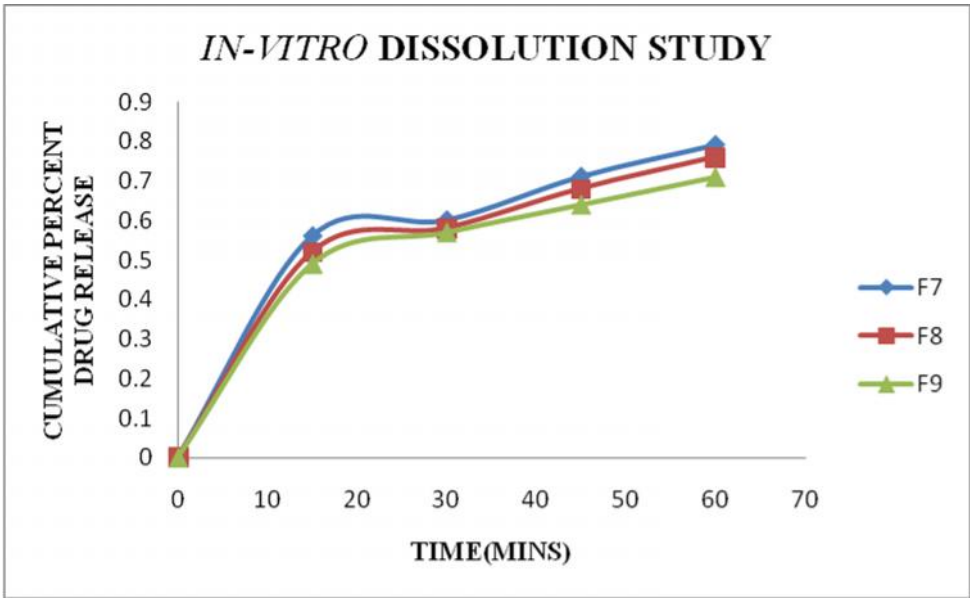


Figure no.37: Cumulative Percentage of Release of Lansoprazole in 0.1N HCL



From the graphs it was observed that the formulation F9 had better resistant to 0.1N HCL as compared to other formulations. And this is because formulation F9 contains high concentration of sugar sphere and HPMC K5 and low concentration of eudragit L30 D 55. As sugar sphere used in high concentration it giving a thin layer of drug on each pellets and HPMC K5 used in high concentration forming a thick layer between drug and enteric polymer, so it prevent the interaction between the drug and enteric polymer. Therefore formulation F9 showed the better resistant to 0.1N HCL.

Figure no.38: Cumulative Percentage of drug Release of Lansoprazole in phosphate buffer pH 6.8

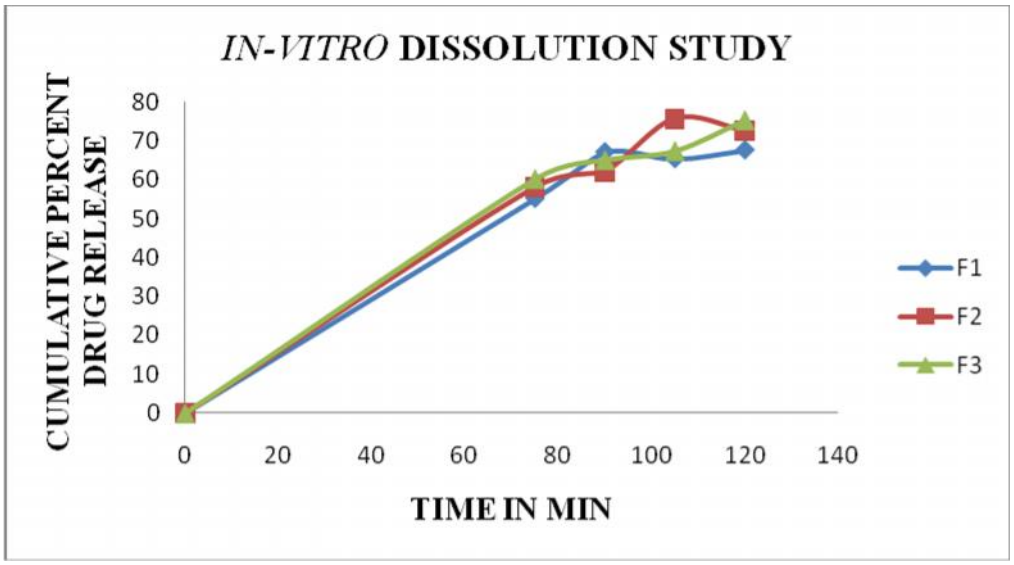


Figure no.39: Cumulative Percentage of drug Release of Lansoprazole in phosphate buffer pH 6.8

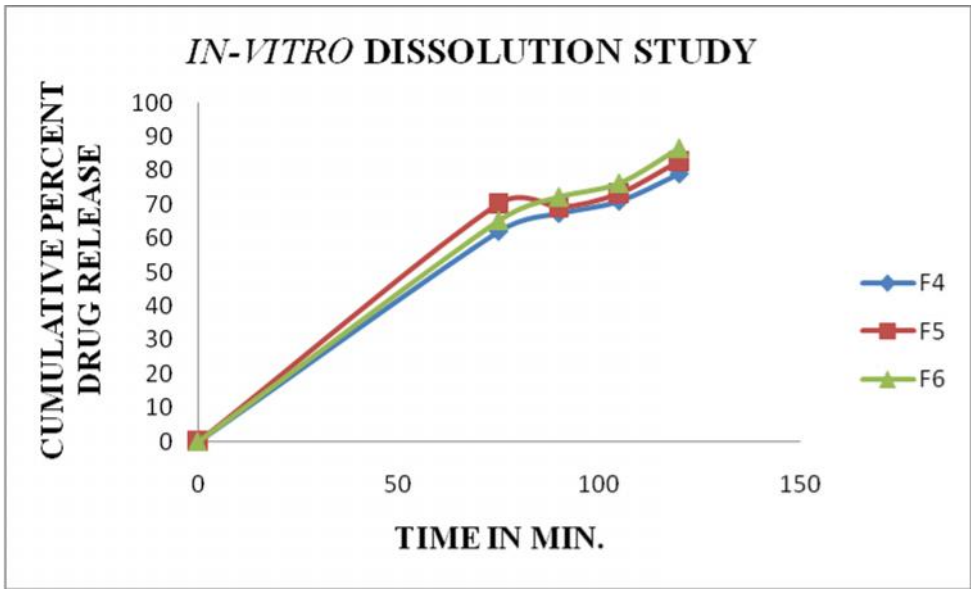
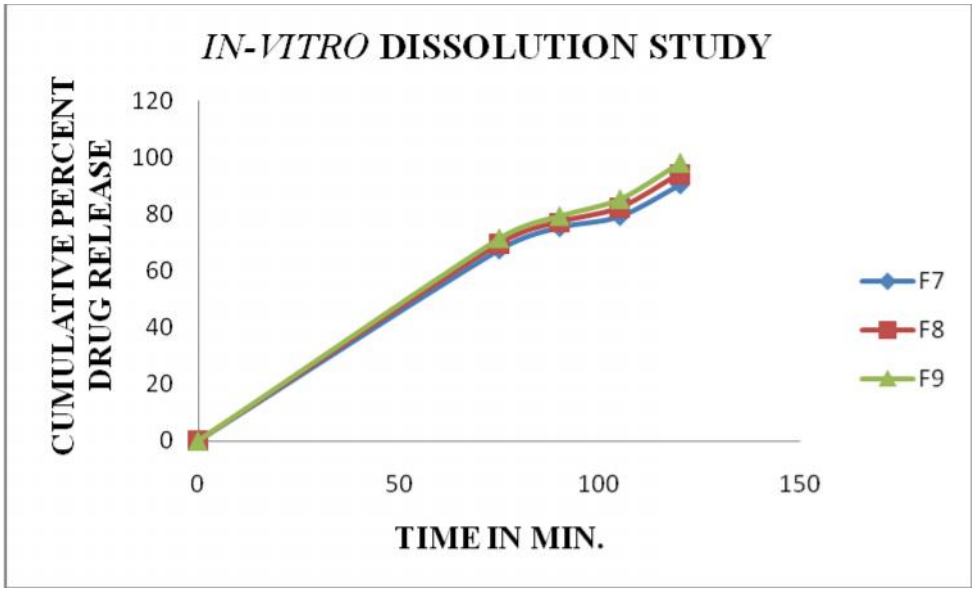


Figure no.40: Cumulative Percentage of drug Release of Lansoprazole in phosphate buffer pH 6.8

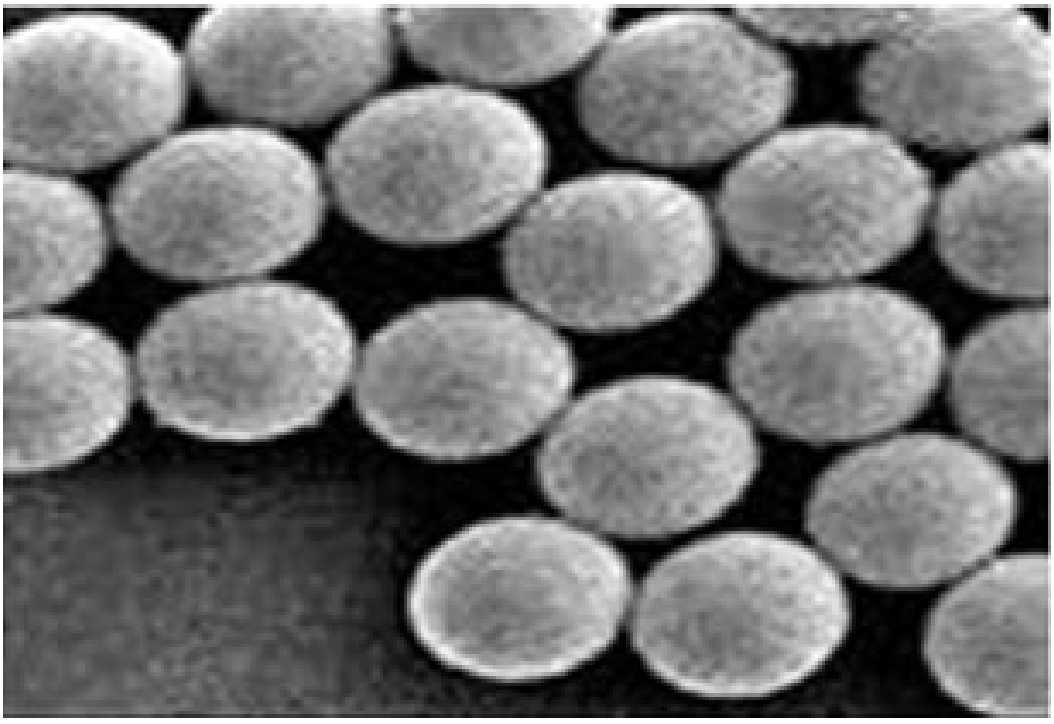


From the results it was observed that the formulation F9 has better cumulative percent drug release as compared to other formulations. Because it may be in formulation F9 Eudragit L30 D55 was used in low concentration, therefore the drug release from pellets occurs fastly in phosphate buffer pH 6.8. While keeping in 6.8 pH buffer, 71.25 cumulative percent drug release occur at 75 minutes, After 120 minutes 97.87 cumulative percent drug release was attained, when compared to other formulation F9 showed better release, so F9 was selected as optimized formulation.

7.3.8. SCANNING ELECTRON MICROSCOPY:

The scanning electron microscopy of formulation F9 showed that prepared pellets have good coating and film former and it is helpful in controlling the release of drug in acidic medium.

Figure no.41: SEM of Formulation F9:



7.3.9. COMPARISON OF INVITRO DISSOLUTION DATA OF OPTIMIZED FORMULATION WITH MARKETED FORMULATION:

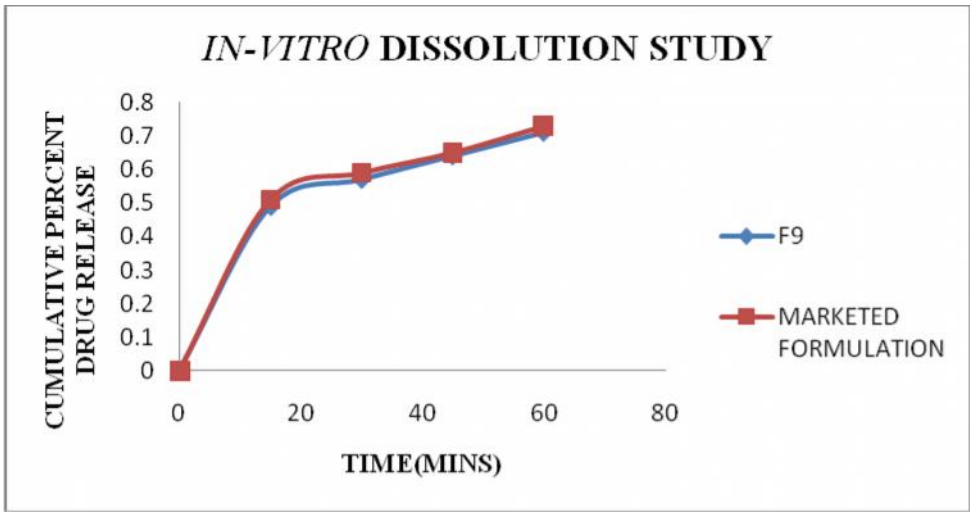
Results for comparison of invitro dissolution data of optimized formulation with marketed formulation were given table no.20 and fig. no.42 and fig. no.43.

Table No.20: comparison of cumulative % drug release in 0.1N HCL and phosphate buffer pH 6.8 of optimized Formulation with marketed product.

1) IN 0.1 N HCL		
TIME IN MIN.	**F9**	**MARKETED FORMULATION**
0	0	0
15	0.49	0.51
30	0.57	0.59
45	0.64	0.65
60	0.71	0.73
2) IN PHOSPHATE BUFFER 6.8		
75	71.25	69.43
90	79.10	78.05
105	85..09	83.54
120	97.87	95.71

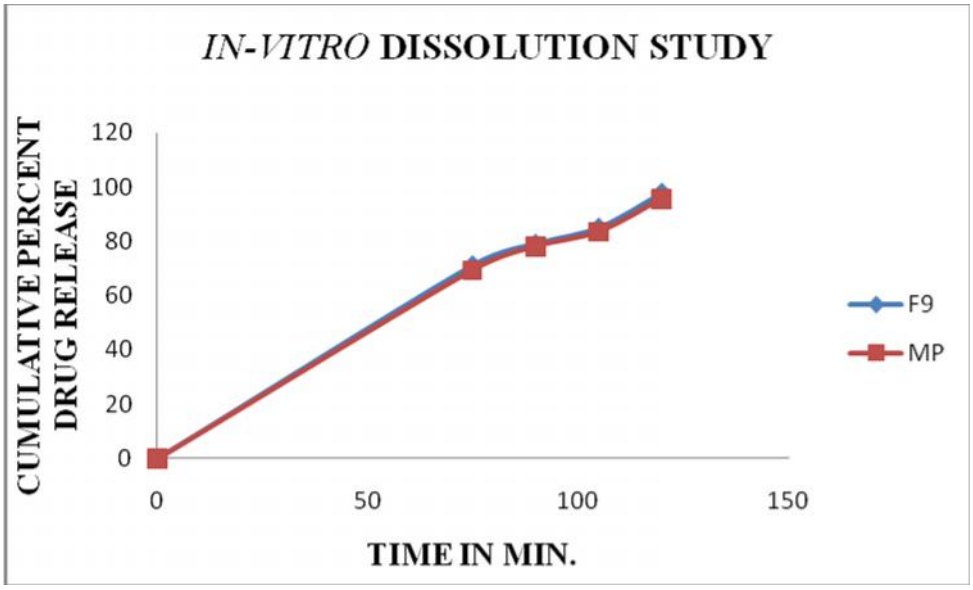
All values represent mean (n) =3.

Figure no.42: Comparison of Dissolution Profile of Optimized Formulation with Marketed Formulation in 0.1 N HCL



Optimized formulation (F9) was compared with the marketed product. The *invitro* values have been obtained in limits compared to the marketed product. By these values concluded that optimized formulation has better resistance to 0.1N HCL compared to the marketed product.

Figure no.43: Comparison of Dissolution Profile of Optimized Formulation with Marketed Formulation



Optimized formulation (F9) was compared with the marketed product. The dissolution values have been obtained and showed the better release of drug as compared to the marketed product in phosphate buffer pH 6.8.

7.3.10. Accelerated stability study

Stability profile of Formulation F9

Table No. 21: Dissolution data of stability

1) IN 0.1 N HCL					
S.No.	**Time(min)**	**Cumulative % drug release**			
		Initial	**1 month**	**2 months**	**3 months**
1	0	0	0	0	0
2	15	0.49	0.46	0.43	0.39
3	30	0.57	0.55	0.53	0.49
4	45	0.64	0.62	0.55	0.51
5	60	0.71	0.69	0.63	0.54
2) **IN PHOSPHATE BUFFER 6.8**					
6	75	68.25	68.25	68.25	68.25
7	90	77.10	77.10	77.10	77.10
8	105	84.09	83.96	83.70	83.65
9	120	97.76	97.73	97.65	97.55

All values represent mean ± standard deviation (SD) n=3.

Figure no.44: Comparison of Dissolution Data of Stability IN 0.1 N HCL

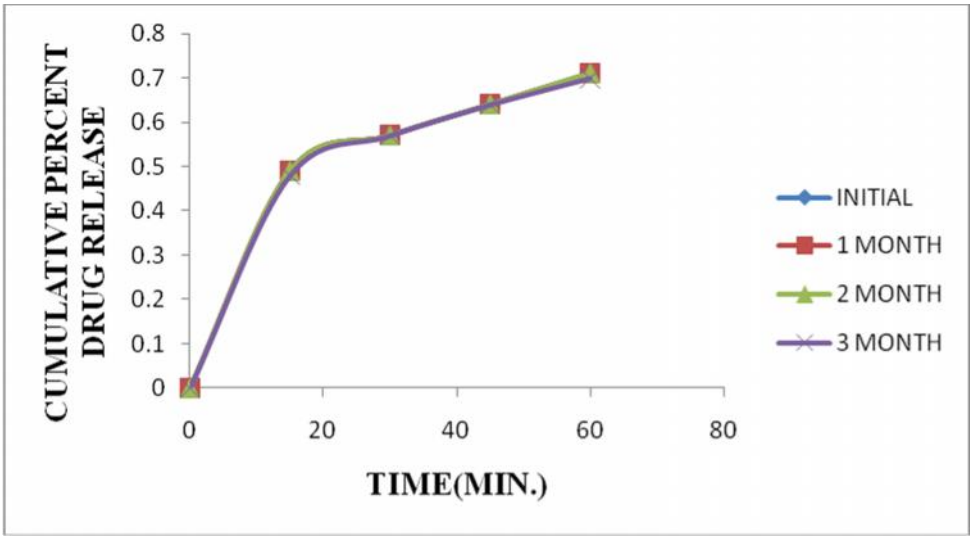
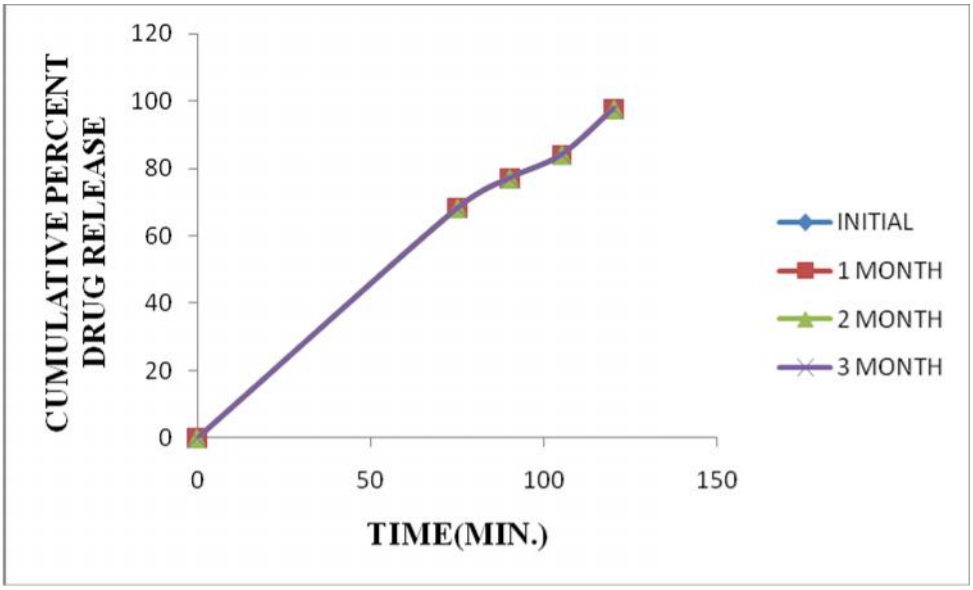


Figure no.45: Comparison of Dissolution Data of Stability IN 0.1 N HCL



After comparison of dissolution data of stability at 0, 1, 2, 3 months there was no changes observed, and clearly showing that the formulated product was stable.

Chapter-8

Summary and Conclusion

8. SUMMARY AND CONCLUSION

The study was undertaken with an aim to develop an optimized formulation of Lansoprazole Enteric Coated Pellets drug delivery system by using Eudragit L-30D-55, HPMC K5 as retarding agents. The active pharmaceutical ingredient, Lansoprazole was selected and formulated as Enteric Coated Pellets comparable to the innovators product.

In the present work, preformulation studies were conducted to know the drug excipients compatibility by using FTIR spectroscopy. Based on the results, suitable excipients were selected for formulation development. FTIR spectra revealed that there was no significant interaction between drug and polymer.

Pellets were prepared by using Suspension layered method. Finished products were evaluated for friability test, assay, and *In-vitro* release studies performed for 1hr in acidic media at 0.1N HCL, after that 1 hr in 6.8 pH Phosphate buffer.

From the evaluation it was concluded that percent friability and percent assay for all formulations from F1 to F9 were found within the limit. *Invitro* dissolution study showed that Formulation F9 having the better resistance in 0.1 N HCL and good release in phosphate buffer pH 6.8.

From the above results and discussion it might be concluded that the formulation F9 of enteric coated pellets of Lansoprazole was found to be stable in acidic medium and shows better drug release in basic medium. Therefore it was an ideal and optimized formulation of enteric coated pellets.

Then the optimized formulation F9 was compared with marketed product by an *invitro* study, it shows that the formulation F9 was good as compared with marketed one.

The stability study was carried out for formulation F9 at 1, 2, 3 month for *invitro* dissolution study and from this it was observed that there were no changes and clearly showing that the optimized formulation F9 was stable.

In future, this work extends for in-vivo study.

Chapter-9

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